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Archives of Internal Medicine

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STUDIES ON ARTHRITIS IN THE ARMY BASED ON FOUR HUNDRED CASES

IV. STUDIES IN THE RELATION OF CREATIN METABOLISM TO ARTHRITIS

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AND

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The researches of the past fifteen years on the chemistry and biochemistry of creatin and creatinin have abundantly established the high importance of these substances in the animal economy, and it seems appropriate at the outset of this paper to present a brief summary of those investigations which have a direct bearing on the subject here considered.

Previous to 1906, general acceptance was given to the theory of the older investigators[1] that the creatinin eliminated in the urine is a waste product derived from muscle creatin. In 1906 Folin published the results of experiments[2] in which he showed that ingestion of creatin did not cause the appearance of creatin in the urine, and did not appreciably influence the elimination of creatinin, from which he concluded that though chemically closely akin, creatin and creatinin are biologically distinct. Since that time numerous observers have confirmed these experiments (Klercker, Wolf, Shaffer) and the metabolic gap between the two substances has grown increasingly wider.[3] Meyers and Fine,[4] on the other hand, have carried out extensive experimental work designed to substantiate the theory that muscle creatin is the

1. Van Hoogenhuyze and Verploegh: Ztschr. f. Physiol. Chem. **46**:416, 1906; Jaffe: Ibid. **48**:430, 1906.
2. Folin: Hammarsten Festschrift, 1906.
3. It seems difficult to accept any definite conclusions regarding the normal fate of creatin in the body from experiments in which massive doses (20 gm.) of creatin are fed and small (from 0.30 to 0.49 gm.) quantities of creatin are recovered from the urine. Rose and Dimmitt: J. Biol. Chem. **26**:346, 1916.
4. Meyers and Fine: J. Biol. Chem. **14**:18, 1913.

precursor of the creatinin eliminated in the urine. They have called attention especially to the close parallelism between the average creatin content of the muscle of a given species and the creatinin coefficient for that species (Mg. of creatinin nitrogen per twenty-four hours per kilogram of body weight). Such data are highly suggestive, but it is difficult to draw incontestable conclusions from this parallelism. In the first place, it is doubtful whether any creatin is set free from the muscles under normal circumstances.[5] Moreover, Folin and Buckman[6] have shown that the creatin content of the muscles of animals of a given species varies within too wide limits to permit of average figures being used in calculation. Finally, as pointed out by Benedict and Osterberg,[7] and Folin and Denis,[8] the creatinin coefficient is a very variable quantity when applied to *different* individuals, owing to the fact that other tissues, notably adipose tissue, not directly concerned with the production of creatinin, influence to a large extent the weight of an animal. At present, then, it would seem that there is no undisputed evidence to show that creatin is, under any conditions so far studied, a precursor of any important part of the creatinin eliminated.

Regarding the significance of urinary creatin, it has been known since the work of Folin in 1905,[9] that the amount of creatinin eliminated on a creatinin-free diet is a constant for a given individual, and is independent of the amount of protein ingested—thus suggesting that the creatinin eliminated is an index of the endogenous or cellular metabolism. The significance of urinary creatinin has been studied by numerous investigators since then, among them Taylor and Rose,[10] Fowler and Hawk,[11] Shaffer,[12] and Meyers and Fine,[13] and the concensus of opinion seems to be that the urinary creatinin represents an end-product of a normal (endogenous) metabolic process taking place chiefly in the muscles, and that the amount eliminated is proportional to the active mass of muscle tissue present (on a creatinin-free diet).

Creatin, as is well known, does not occur, or occurs only in very small traces, in the urine of normal adult males on an ordinary diet. Its occurrence in a great variety of pathologic conditions and conditions of altered metabolism (fevers, starvation, carcinomatosis, acidosis, faulty carbohydrate ultilization, high protein feeding, child-

5. Folin and Denis: Ibid. **17**:493, 1914.
6. Folin and Buckman: Ibid. **17**:183, 1914.
7. Benedict, S. R., and Osterberg, E.: J. Biol. Chem. **18**:195, 1914.
8. Folin and Denis: Loc. Cit.
9. Folin: Am. J. Physiol. **13**:118, 1905.
10. Taylor anl Rose: J. Biol. Chem. **14**:419, 1913.
11. Fowler and Hawk: J. Exper. M. **12**:388, 1910.
12. Shaffer: Quoted by Hawk, Pract. Physiol. Chem., 1918, p. 490.
13. Meyers and Fine: J. Biol. Chem. **14**:388, 1913.

hood, pregnancy, massive doses of creatin) has formed the basis of a large number of reasearches regarding the origin of creatin and its relation to creatinin.

There are several hypotheses advanced to account for the appearance of creatin in the urine in various conditions. F. B. Benedict,[14] who was the first to report creatinuria in starving men, suggested that the creatin is derived from muscle creatin. This problem has been further studied by Mendel and Rose,[15] and by Myers and Fine,[16] and the latter observers concluded from their experiments that the creatin of the urine in starvation owes its origin to the disintegration of muscle tissue. But, as Benedict (S. R.) and Osterberg[17] suggest, disintegration of muscle tissue may mean either a selective liberation of creatin or a more or less complete destruction of the proteins of the tissue. From the experiments of Folin and Denis,[18] it is difficult to see how any selective liberation of creatin can occur. The last named investigators showed from observations on the absorption of creatin from the blood by living muscle, that living muscle contains practically no creatin, and concluded "that the creatin found on analysis is a post-mortem product originally constituting a part of the living protoplasm." On the other hand, as pointed out by Benedict and Osterberg, if an actual destruction of muscle protoplasm does occur, and the creatin is split off as such during the process of destruction, we should expect that the total nitrogen of the urine would closely parallel the creatin eliminated (or creatin plus creatinin). These experiments[19] showed, however, that a high creatin elimination could be maintained which was independent of the tissue destroyed. Benedict and Osterberg worked with completely phlorizinized dogs, sparing the body proteins by feeding the necessary amount of creatin-free protein. The animals were fasted for a preliminary period of two or three days before the injections of phlorizin were begun, and in some cases the fasting was continued after the injections of phlorizin had been begun. That is, the animals were first subjected to simple starvation, then to greatly "intensified starvation" (phlorizin), and were then kept in nitrogen equilibrium (or nearly so) by feeding creatin-free protein to spare the body proteins. The creatin elimination, slight during simple fasting, increased markedly on administration of phlorizin (intensified starvation) and then showed a decline, unless an adequate supply of protein was furnished, but throughout was independent of the body

14. Benedict, F. G.: Carnegie Institute, Washington, Pub. 77, 1907, p. 386.
15. Mendel and Rose: J. Biol. Chem. **10**:213, 1911.
16. Meyers and Fine: Ibid. **15**:283, 1913.
17. Benedict, S. R., and Osterberg, E.: J. Biol. Chem. **18**:195, 1914.
18. Folin and Denis: Ibid. **17**:493, 1914.
19. Benedict and Osterberg: Loc. Cit.

TABLE 1.—Results of Analyses of Normal Controls and Arthritis Patients

Case	Name	Registration No.	Urine, Gm. per 24 Hours								Blood, Mg. per 100 C.c.			Remarks
			Age	Weight	Date	Creatin	Creatinin	Mg. Creatinin Nitrogen per Kg.	Total Nitrogen	Percentage Nitrogen as Creatinin	Total Non-protein Nitrogen	Creatin	Creatinin	
Control	Canf.	1	22	68.5	3/16	0.0	1.40	7.6	8.24	6.3	26.0	3.7	1.2	Normal man
Control	Huds.	2	24	84.0	3/16	0.0	1.72	7.5	6.42	10.0	27.4	4.2	1.3	Normal man
Control	Edde.	3	25	65.0	3/16	0.0	1.65	9.4	7.26	8.4	28.2	4.8	1.1	Normal man
Control	Buck.	4	27	62.3	5/10	0.0	1.45	8.7	9.98	5.5	30.7	4.6	1.0	Normal man
Control	Boll.	5	24	74.2	5/10	0.0	2.18	11.0	10.20	7.9	28.8	3.7	1.1	Normal man
Control	Fiel.	6	25	63.7	5/12	0.0	1.85	10.6	9.18	7.3	29.0	4.6	0.6	Normal man
Control	Edw.	7	22	62.0	5/12	0.0	1.60	9.5	10.82	7.9	27.8	4.0	0.8	Normal man
Control	Strick.	8	26	61.0	5/15	0.0	1.35	8.3	7.80	6.5	25.3	4.5	0.8	Normal man
Control	Boda.	9	23	57.7	5/15	0.0	1.01	6.5	7.20	5.3	30.9	5.0	0.8	Normal man
	Averages	.....	24	66.5	....	0.0	1.58	8.8	8.53	7.26	28.4	4.3	1.0	
64	Fish.	3689	23	62.0	5/ 1	0.0	1.25	6.9	6.87	6.8	30.9	2.9	0.9	Convalescent, ambulatory
65	Gal.	5245	28	65.0	3/ 4	0.0	1.38	7.8	7.90	6.5	23.0	3.4	1.6	Convalescent, ambulatory
66	Bass.	3888	21	61.3	5/ 2	0.0	0.93	5.1	6.58	5.2	29.5	3.5	1.3	Chronic tonsillitis, tuberculous arthritis
67	Burg.	3556	23	62.3	4/28	0.48*	1.28	7.7	12.32	3.9	19.5	3.6	1.8	Convalescent, ambulatory
68	Turn.	3982	31	75.0	4/29	0.0	1.90	9.4	16.24	4.4	22.2	3.7	1.3	Convalescent, ambulatory
48	Jans.	4238	32	58.2	5/ 5	0.0	1.37	8.7	8.15	6.2	30.8	3.9	1.0	Convalescent, ambulatory
69	McInt.	4481	21	63.5	4/ 1	0.0	1.62	9.5	11.32	5.3	28.2	4.0	4.6	Convalescent, ambulatory
6	Hay.	1699	29	54.8	5/ 3	0.0	0.90	6.2	6.69	5.0	24.0	4.0	1.1	Convalescent, ambulatory
70	Font.	3809	20	58.0	5/ 7	0.0	1.16	7.2	9.76	4.3	28.8	4.0	0.7	Tuberculous spine (?)
46	Heth.	4257	40	85.0	5/11	0.0	1.44	6.3	10.21	5.6	27.4	4.1	0.9	Convalescent, ambulatory
71	Craw.	4567	30	54.6	4/29	0.0	1.31	9.4	7.42	6.6	20.2	4.2	1.5	Severe, chronic, bed
72	Bark.	4053	27	61.3	5/ 2	0.0	1.37	6.1	8.34	6.2	28.3	4.2	1 4	Chronic otitis media, (?) tuberculous, pleural and pericardial adhesions, ulcers of leg

52	Lyn.	4836	32	61.5	5/13	0.0	1.30	7.9	6.16	7.9	26.5	4.4	0.8	Convalescent, ambulatory
73	Jor.	5294	20	63.5	5/ 1	0.0	1.48	7.7	9.00	6.1	30.6	4.4	0.9	Convalescent, ambulatory
74	Cur.	5351	32	56.3	5/ 9	0.0	2.08	13.3	7.74	9.8	22.5	4.4	0.9	Convalescent, ambulatory
75	Dio.	4828	30	66.8	4/22	0.0	1.41	7.3	8.20	6.3	25.7	4.5	1.0	Convalescent, ambulatory
76	Hick.	4803	47	74.5	5/14	0.0	1.09	5.4	6.47	6.3	25.5	4.5	1.0	Convalescent, ambulatory
1	Rob.	5054	26	78.7	4/26	0.0	1.46	6.9	5.72	9.4	19.8	4.7	1.4	Convalescent, ambulatory
59	Flan.	5252	27	68.3	4/12	0.0	1.22	6.6	5.61	8.0	25.1	4.8	1.1	Convalescent, ambulatory
77	Morr.	5443	26	65.8	5/11	0.0	1.15	6.5	7.37	4.1	24.8	4.8	1.0	Convalescent, ambulatory
63	Fol.	4919	24	64.2	4/22	0.0	1.71	10.6	12.83	4.5	30.9	4.9	1.0	Convalescent, ambulatory
55	Cott.	4–11	34	70.3	4/18	0.0	1.80	9.2	11.21	6.0	27.9	4.9	1.3	Convalescent, ambulat'ry, mild
78	Kirk.	4997	23	59.2	5/ 5	0.0	1.53	6.7	10.00	5.7	27.4	4.9	1.4	Convalescent, ambulatory
46	Heth.	4257	40	85.0	4/ 2	0.0	2.68	11.7	12.52	8.0	28.2	5.0	1.8	Convalescent, ambulatory
20	Wass.	3658	21	60.0	4/ 7	0.0	1.06	6.6	6.58	5.9	29.0	5.0	1.5	Severe, chronic, bed
7	Jaff.	1525	24	55.4	3/27	0.0	1.33	9.2	6.73	7.7	28.2	5.0	1.8	Chronic, level, ambulatory
62	McKen.	4973	20	57.0	4/30	0.0	1.82	12.0	8.18	8.3	28.5	5.0	1.2	Acute attack, bed, febrile
79	Cox.	2477	36	65.5	4/18	0.0	1.63	9.3	7.12	8.5	28.3	5.2	1.3	Convalescent, ambulatory
47	Chan.	4049	26	68.2	5/ 8	0.0	0.89	4.8	10.80	3.0	24.9	5.2	0.8	Convalescent, ambulatory
60	Herr.	4804	24	67.4	4/20	0.0	1.70	9.3	6.07	10.3	22.1	5.4	1.4	Acute attack, bed
61	Mill.	5313	22	53.6	5/13	0.0	1.36	8.9	10.82	4.7	30.7	5.4	0.9	Convalescent, ambulatory
8	Mart.	4805	45	82.0	3/26	0.0	0.91	4.2	4.65	7.3	45.4	5.5	0.7	Chronic, severe, bed
11	Hin.	2503	25	56.4	4/14	0.0	1.42	9.2	5.80	9.0	31.9	5.5	1.4	Convalescent, ambulatory
88	Spat.	4479	22	78.3	5/ 3	0.0	0.79	3.7	5.08	5.6	26.3	5.7	1.0	Tuberculous arthritis (†)
22	Obe.	3712	24	61.2	5/14	0.0	1.45	9.0	8.79	6.1	26.3	5.7	1.0	Convalescent, ambulatory
49	Kotse.	3899	25	64.0	4/ 4	0.0	1.52	8.8	11.00	5.1	28.6	5.8	0.8	Chronic, severe, bed
11	Hin.	2503	25	56.0	3/31	0.0	1.56	10.4	7.58	7.4	28.6	5.9	1.1	Convalescent, ambulatory
52	Lyn.	4836	32	61.5	4/17	0.0	1.03	6.3	4.60	8.4	30.9	6.0	1.3	Convalescent, ambulatory
48	Jan.	4238	32	59.5	4/ 7	0.0	1.86	11.6	6.46	10.8	26.2	6.0	5.2	Convalescent, ambulatory
61	Mill.	5313	22	53.7	4/24	0.0	1.39	9.7	9.16	5.7	24.1	6.6	0.8	Acute attack, febrile
53	Kal.	....	42	71.8	5/ 9	0.0	1.46	7.7	7.23	7.5	29.1	6.8	1.1	Chronic, ambulatory
14	Low.	3550	42	72.3	4/ 7	0.1†	1.52	7.8	6.26	8.9	30.0	7.0	0.7	Chronic, ambulatory
57	Lang.	4670	21	57.3	4/12	0.0	0.86	5.6	4.08	7.8	38.5	7.0	0.9	Chronic, ambulatory
47	Chan.	4049	26	69.2	4/14	0.16‡	1.76	9.4	10.45	6.3	34.5	7.0	1.5	Chronic, ambulatory
47	Chan.	4049	26	67.0	4/20	0.40§	1.06	5.8	6.90	5.6	27.1	7.1	1.2	Acute attack, bed
62	McKen.	4973	20	57.0	4/15	0.0	1.43	9.3	4.80	11.0	30.9	7.3	0.7	++ Wassermann
81	Sehn.	3899	25	61.0	4/26	0.0	1.30	7.9	6.72	7.4	23.1	7.3	1.7	Chronic, ambulatory
48	Jan.	4238	32	59.5	3/27	0.0	1.95	12.4	10.40	6.9	24.0	7.8	6.0	Chronic, ambulatory
76	Hick.	4803	47	74.5	4/12	0.0	1.49	7.4	7.25	7.6	22.9	7.8	1.2	Chronic, ambulatory
7	Jaff.	1525	24	56.4	4/12	0.0	1.26	8.4	4.10	8.7	30.8	7.9	1.0	Chronic, ambulatory
	Averages	.....	..	....	....	0.023	1.41	8.1	8.00	5.27	27.6	5.27	1.4	

* Plasma creatin 1.3 † Plasma creatin 3.0 ‡ Plasma creatin 3.3 § Plasma creatin 3.1

nitrogen lost. The quantity of creatin eliminated during starvation, then, is independent of the amount of tissue destroyed, and this creatin does not come from preformed creatin split off in the process of destruction. There still remains the possibility, however, that the creatin eliminated during starvation may be synthesized from the end-product of the destruction of muscle protein. In this case, the quantity synthesized, and hence the quantity eliminated, would not necessarily be directly proportional to the amount of tissue destroyed (total nitrogen) even though the utilization of creatin were completely (?) inhibited (phlorizin).

It has recently been suggested by Hunter and Campbell[20] that there may be a threshold for the elimination of creatin, and that certain cases of creatinuria may be accounted for on this basis. They have published results of the simultaneous determination in the blood plasma and urine from which they conclude "that the concentration of creatin in the urine bears a direct relation to that in the plasma, and that a slight increase in the latter (as little as 0.1 mg. per hundred c.c.) suffices to bring about a copious secretion." These observers suggest the interesting possibility of the dependence of creatinuria on a specific increase in renal permeability. While the theory of a threshold for creatin elimination is entirely plausible, it is difficult to see how reliable conclusions with respect to such small amounts of creatin can be drawn with the use of any of the current methods for the determination of creatin in plasma.

The relationship of creatinuria to excessive protein feeding has been repeatedly demonstrated during the last five years. Amberg and Morrill,[21] Rose,[22] and Folin and Denis[23] have shown that creatinuria is a constant finding in children up to puberty. Folin and Denis,[24] and Denis and Kramer[25] have presented highly important experimental data showing that the "creatin found in the urine of children is directly dependent on the intake of protein (creatin-free), being high when large quantities of protein are ingested, decreasing and in some cases disappearing entirely when the child is fed a diet of an extremely low protein content." Denis and Kramer point out further, that "the low saturation point of immature muscle suggested by the small creatin content of the muscles of children, and the relatively low level of protein consumption at which creatin is excreted, may account in part for the creatinuria." The relationship of high protein feeding to

20. Hunter and Campbell: J. Biol. Chem. **33**:188, 1918.
21. Amberg and Morril: Ibid. **3**:311, 1907.
22. Rose, W. C.: Ibid. **10**:265, 1911.
23. Folin and Denis: J. Biol. Chem. **11**:253, 1912.
24. Folin and Denis: Ibid., Loc. Cit.
25. Denis and Kramer: J. Biol. Chem. **30**:189, 1917.

creatinuria has been further studied by McCollum and Steenbock[26] working with pigs and by Denis and Minot[27] working with adult women and persons suffering with hyperthyroidism.

On the other hand, Rose, Dimmitt and Bartlett[28] were unable to produce creatinuria on the amount of protein that they gave their subjects but, as pointed out later by Denis and Minot,[29] it is necessary to give much more protein (as much as 33 gm. of nitrogen per twenty-four hours) than Rose, Dimmitt and Bartlett gave, and it is also desirable to precede the period of excessive protein intake by a period of high protein feeding.

That the creatinuria of excessive protein intake might be due to an acidosis caused by the highly acid character of the protein diets, has been amply precluded by recent work of Denis and Minot[30] who have shown that the creatinuria persists unaltered, even though the urine is kept alkaline (administration of sodium bicarbonate) and by the work of Steenbock and Gross[31] who have shown that sufficiently high protein diets will always produce creatinuria in pigs, even in the presence of alkalosis.

Although Cathcart and Taylor,[32] from experiments on partially phlorizinized dogs, were led to conclude that the processes leading to acidosis and creatin elimination are distinct, nevertheless, Underhill[33] has shown that creatinuria would make its appearance in rabbits fed on diets rich in acid salts or on basic diets, to which hydrochloric acid had been added and would disappear on feeding basic diets. Moreover, Underhill and Bauman,[34] working with animals to which they administered hydrazin sulphate, were able to demonstrate creatinuria both in the presence of acidosis and a normal carbohydrate intake and in the absence of acidosis in the presence of hypoglycemia.

Unfortunately, most of the observations on creatinuria and acidosis have been confused by the presence of carbohydrate starvation, so that it cannot be regarded as settled that acidosis alone is capable of producing creatin elimination.[35]

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26. McCollum and Steenbock: Ibid. **13**:209, 1912.
27. Denis and Minot: Ibid. **21**:561, 1917.
28. Rose, Dimmitt and Bartlett: Ibid. **24**:601, 1918.
29. Denis and Minot: Loc. Cit.
30. Denis and Minot: **37**:245, 1919.
31. Steenbock and Gross: J. Biol. Chem. **36**:265, 1918.
32. Cathcart and Taylor: J. Physiol. **41**:276, 1910.
33. Underhill, F. P.: J. Biol. Chem. **27**:127, 1916.
34. Underhill and Bauman: Ibid. **27**:151, 1916.
35. Many of the reported findings of creatin in urines (and bloods) containing aceto-acetic acid are doubtful inasmuch as the aceto-acetic acid causes too low results for creatinin. On boiling, the acid is destroyed and a higher value is obtained which may be taken for creatin.

In 1907, Cathcart[36] first suggested a relationship between faulty carbohydrate metabolism and the elimination of creatin. The relationship has been further studied by Underhill and Kleiner,[37] who showed that hydrazin sulphate caused a marked hypoglycemia and creatinuria, by Mendel and Rose,[38] who showed that carbohydrate food administered to starving rabbits showing creatinuria would immediately cause the cessation of the creatin elimination, whereas protein would not, and by Rose,[39] Wolf[40] and S. R. Benedict and Osterberg.[41] The last named investigators, whose work is quoted above, carried out an extensive series of experiments on phlorizinized dogs, from which they concluded that "the power of the organism to metabolize the creatin which it forms is directly related to certain other processes, chief among which appears to be the utilization of carbohydrate."

The bulk of evidence in regard to the origin and fate of creatin would seem to indicate that that substance is not derived from preformed creatin of muscle as once believed, but rather that it is constantly being formed in the body, possibly synthesized from the amino-acids produced in the intermediary metabolism of proteins, whether these come from the food or the body (starvation), and is, under normal cricumstances, being retained in the body or utilized for constructive purposes. It may be eliminated in the urine when produced in excess of the absorption capacity of muscles (high protein feeding in childhood), possibly in uncomplicated acidosis, and when its retention or utilization is inhibited by factors that interfere with the utilization of carbohydrate (fasting and the more complete forms of carbohydrate starvation [phlorizin] and in diabetes mellitus[43]). There is no

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36 Cathcart: J. Physiol. **25**:500, 1907.

37. Underhill and Kleiner: Quoted by Underhill and Bauman, J. Biol. Chem. **27**:151, 1916.

38. Mendel and Rose: Ibid. **10**:213, 1911.

39. Rose, W. C.: Ibid. **10**:265, 1911.

40. Wolf: Ibid. **10**:473, 1912.

41. Benedict, S. R., and Osterberg, E.: J. Biol. Chem., Loc. Cit.

42. Wolf (J. Biol. Chem. **10**:473, 1912) has shown that feeding of protein to starving dogs causes a disappearance of the creatinuria and, more recently, Rose, Dimmitt and Cheatham (J. Biol. Chem. **26**:339, 1916) have shown that by feeding protein to starving men the creatin output can be reduced to nil. These findings in no way vitiate the hypothesis that carbohydrate food is necessary for the retention or utilization of creatin inasmuch as Lusk has shown that a considerable part of the protein in starving dogs and men is converted into carbohydrate (glucose).

43. Numerous attempts have been made to determine the origin of creatin by feeding a possible precursor, as for example, arginin (Inouye), guanidin acetic acid (Jaffe), cholin and lecithin (Koch). Owing to the fact that large amounts of creatin can be ingested without the production of creatinuria, it would seem that any attempt to feed a precursor of creatin and recover creatin in the urine should be doomed to failure, inasmuch as the body would take care of any creatin formed just as it does the ingested creatin.

undisputed evidence to show that any important part of the creatin formed in the body is converted into creatinin.

In 1918, Janney and Isaacson[44] demonstrated a marked glucose intolerance in cases of hyperthyroidism, and a definite and more or less characteristic glucose intolerance has been demonstrated by Pemberton and Foster[45] in cases of arthritis. Inasmuch as creatinuria has been demonstrated in hyperthyroidism (after high protein feeding) and in other conditions where there is a disturbance in the body's capacity to utilize carbohydrate, it was deemed worth while to investigate a series of arthritics with a view of determining the presence of abnormalities in the metabolism of creatin as revealed by blood and urine analysis. It was planned to study cases first on an average diet and then on diets containing no carbohydrates and an excess of protein with and without creatin added. Owing to the closing of the hospital, it was not possible to complete these investigations as originally planned, but the data collected seemed to be of sufficient technical and general medical interest to warrant publication.

METHODS

(a). *Description.*—The determinations of creatin and creatinin in blood and plasma were made by the methods of Folin,[46] the picric acid solution being precipitated and made alkaline by the use of the potassium hydroxid-potassium chlorid mixture recommended by Folin and Doisy.[47] The determination of creatin in urine was made by the Folin method.[48] The conversion of urinary creatin into creatinin was effected by the autoclave procedure of Meyers and Benedict.[49] Several determinations of picric acid on blood were made by the Denis method and these also are reported.[50] For the determinations of total nonprotein nitrogen in both blood and urine, the direct nesslerization method of Folin and Denis was used.[51] Considerable difficulty was experienced

44. Janney and Isaacson: Arch. Int. Med. **22**:160 (Aug.) 1918.

45. Pemberton and Foster: Part III, Studies on Arthritis in the Army, Arch. Int. Med. **25**:243 (March) 1920.

46. Folin: J. Biol. Chem. **17**:475, 1914.

47. Folin: Ibid. **27**:349, 1916.

48. Folin: Ibid. **17**:164, 1914.

49. Benedict, S. R.: Ibid. **18**:191, 1914. The creatinin used in preparing the standard solutions was presented to the laboratory through the courtesy of Prof. S. R. Benedict. The standard solutions were kept in dark glass bottles and no standard over six weeks old was used. (See Hunter and Campbell: J. Biol. Chem. **28**:335, 1916.)

50. Denis: J. Biol. Chem. **35**:513, 1918.

51. Folin and Denis: Ibid. **26**:491, 1916. It was found that the metaphosphoric acid with which we coagulated the proteins contained a small amount of nitrogen, sufficient to elevate the total nonprotein nitrogen by from 1.8 to 2.6 mg. per hundred c.c. of blood. The proper deduction was made in each case. Since the analyses were made, Folin has pointed out (personal communication, May 19, 1919) that this nitrogen can be removed by fusing 100 gm. of the metaphosphoric acid with from 1 to 2 gm. of potassium nitrate.

TABLE 2.—Determination of Creatin and Creatinin in Blood and Urine of Arthritis Patients

Name Case Registration No. Operation	Date	Urine. Gm. per 24 Hours					Blood, Mg. per 100 C.c.			Clinical Data
		Total Nitrogen	Creatinin	Creatinin Nitrogen, Weight	Creatin	Creatinin Nitrogen: Total Nitrogen	Whole Blood Creatinin	Whole Blood Creatin		
Jaf. Case 7 Reg. No. 1525 Tonsillectomy 1913	3/27/19	6.73	1.33	9.15	0.0	7.29	3.0	3.8	30.0	Subacute, ambulatory; pain in knees and heel
	4/12/19	4.10	1.26	8.37	0-0	8.73	1.0	7.9	30.8	Considerable improvement since last test
Hin. Case 11 Reg. No. 2503 Tonsillectomy 4/3/19	3/31/19	7.58	1.56	10.40	0.0	7.68	1.1	5.9	28.6	Subacute, ambulatory; chronic tonsillitis
	4/14/19	5.80	1.42	9.23	0.0	8.97	1.4	5.5	31.9	Some improvement
Jan. Case 48 Reg. No. 4238	3/27/19	10.40	1.05	12.40	0.0	6.91	6.0	7.82	24.0	Chronic, ambulatory; walks with cane
	4/14/19	6.46	1.86	11.60	0.0	10.80	5.2	6.0	26.2	Slight improvement since last week
	5/ 5/19	8.15	1.37	8.68	0.0	6.23	1.1	3.9	30.8	Marked improvement; can walk without cane
Cha. Case 47 Reg. No. 4049 Tonsillectomy 3/12/19	4/14/19	10.45	1.76	9.39	0.16	6.22	1.5	7.0	34.5	Chronic; ambulatory, with crutches
	4/22/19	6.90	1.06	5.84	0.40	5.64	1.2	7.1	27.1	Acute attack; in bed; no fever
	5/ 8/19	10.80	0.89	4.76	0.0	3.03	0.8	5.2	24.9	Symptoms still present but much improved
Hic. Case 76 Reg. No. 4808	4/12/19	7.25	1.40	1.38	0.0	7.58	1.2	7.8	22.9	Subacute, ambulatory
	5/14/19	6.47	1.09	5.40	0.0	6.25	1.0	4.5	25.5	Symptoms still persist but definitely improved
McK. Case 62 Reg. No. 4073	4/15/19	4.80	1.43	9.34	0.0	11.00	1.3	7.30	30.9	Chronic, ambulatory
	4/30/19	8.18	1.82	11.95	0.0	8.25	1.2	5.03	28.5	Acute attack; in bed; CO_2 40.4 vol. per cent. acetylsalicylic acid t. i. d. during 3 days of test; febrile
Lyn. Case 52 Reg. No. 4836 Tonsillectomy 4/7/19	4/17/19	4.60	1.03	6.25	0.0	8.38	1.4	6.00	30.9	Chronic, ambulatory
	5/13/19	6.16	1.31	7.90	0.0	7.90	0.8	4.4	29.0	Marked improvement
Mil. Cast 61 Reg. No. 5313 Tonsillectomy 5/1/19	4/24/19	9.16	1.39	9.73	0.0	5.70	0.77	6.6	24.1	Acute attack; in bed; Temp. 100 first day of diet; acetylsalicylic acid t. i. d. for 3 days of diet
	5/13/19	10.82	1.39	8.86	0.0	4.68	0.9	5.4	30.7	No symptoms
Her. Case 60 Reg. No. 4804	4/20/19	6.07	1.70	9.30	0.0	10.30	1.4	5.4	22.1	Acute attack; in bed
Lo.; Case 14 Reg. No. 3530	4/ 7/19	6.26	1.52	7.75	0.097	8.94	0.7	7.0	30.0	Chronic; in bed
	5/ 9/19	7.23	1.46	7.70	0.0	7.51	1.1	6.8	29.1	No improvement

in securing pure picric acid. Samples from four different manufacturers were tested, and all of them, until purified, proved unsatisfactory on account of the marked darkening which took place on boiling, autoclaving, or on neutralizing with alkali. The several samples were purified twice by the method suggested by Folin and Doisy.[52] Only those samples were used for the preparation of standards or for analysis whose color became less than half again as intense on neutralizing with alkali, which showed no change of color on autoclaving and to which creatin could be added, the solution autoclaved, and the creatin recovered quantitatively (colorimetrically) as creatinin.

TABLE 3.—Creatin and Creatinin Values for Whole Blood and Plasma (Folin Method) *

Registration Number	Date	Creatin		Creatinin	
		Whole Blood	Plasma	Whole Blood	Plasma
3689	5/ 1	2.9	1.5	0.9	0.8
3550	4/28	3.6	1.3	1.8	1.3
4238	5/ 3	3.9	2.2	1.0	1.4
1699	5/ 3	4.0	1.3	1.1	0.9
4257	5/11	4.1	1.9	0.9	0.8
6	5/12	4.6	1.3	0.6	0.8
4	5/10	4.6	1.5	1.0	1.0
5054	4/26	4.7	3.0	1.5	1.4
5443	5/11	4.8	1.8	1.0	0.7
4997	5/ 5	4.9	1.8	1.4	1.5
4973	4/30	5.0	2.7	1.2	1.0
4804	4/26	5.2	2.7	1.4	1.6
2503	3/31	5.9	2.5	1.1	1.0
4238	4/ 7	6.0	2.4	5.2	4.8
4836	4/17	6.0	2.2	1.3	1.1
3559	5/ 9	6.8	3.0	1.1	1.0
4049	4/14	7.0	3.3	1.5	1.6
3559	4/ 7	7.0	3.0	0.7	1.0
5313	4/24	7.0	1.7	0.8	0.8
Averages	....	5.4	2.2—	1.3	1.2

* Values for creatin and creatinin are mg. per hundred c.c. of whole blood or plasma.

(b). *Discussion.*—It appears to be fairly definitely settled that determinations on both whole blood and plasma by the Folin method and presumably also by the Denis method, represent the truth so far as creatinin is concerned. Yet it is equally true that when values for creatin in blood or plasma are published, they constitute a casus belli.

In concurrence with the work of Hunter and Campbell,[53] our results show a fairly uniform distribution of creatinin between plasma and corpuscles (whole blood) (Table 3). Moreover, our values for creatin in the plasma are lower, as were theirs, than the values for creatin in whole blood, markedly and uniformly so throughout the entire series. A striking fact about these creatin values is that the values for plasma do not parallel at all the figures for whole blood.

52. Folin and Doisy: J. Biol. Chem. **27**:349, 1916.
53. Hunter and Campbell: Ibid. **33**:169, 1918.

A number of determinations were also made by the Folin method and by the Denis method (Table 4) on the same sample of whole blood. In agreement with Denis' work,[54] our values for creatinin are slightly lower and those for creatin markedly lower by the Denis method than by the Folin method. However, in attempting to apply the metaphosphoric acid precipitation method to plasma, we found, in many instances, extremely small values for creatin—in some cases less than 0.5 mg. per hundred c.c. This observation and the finding of

TABLE 4.—COMPARATIVE ANALYSES OF WHOLE BLOOD FOR CREATIN AND CREATININ BY THE FOLIN AND BY THE DENIS METHOD

Sample	Creatin		Creatinin	
	Folin Method	Denis Method	Folin Method	Denis Method
27	6.0	2.5	1.4	1.3
28	5.2	2.3	1.3	1.3
29	4.9	2.8	1.5	1.2
30	4.5	3.4	1.2	1.0
31	7.1	3.5	1.2	1.0
32	4.8	3.0	1.2	1.2
33	6.6	3.3	0.8	1.4
34	6.1	3.8	1.7	1.9
35	4.7	1.8	1.4	1.8
36	5.4	2.5	1.4	1.4
37	3.6	2.6	1.8	1.6
38	3.4	3.2	1.6	1.8
39	3.8	1.8	1.3	0.9
40	4.2	2.5	1.5	1.4
41	5.0	2.1	1.2	0.6
42	2.9	2.9	0.9	1.0
43	4.4	3.0	0.9	0.7
44	4.2	1.8	1.4	1.2
45	3.5	2.1	1.3	1.4
46	5.7	1.8	1.0	0.9
47	4.0	1.3	1.1	1.0
48	3.9	1.5	1.0	0.9
49	4.9	2.4	1.4	1.4
50	4.0	3.6	0.7	1.5
51	5.2	2.5	0.8	1.0
52	4.4	2.3	0.9	1.1
5	4.6	2.0	1.0	1.0
4	3.7	2.4	1.1	1.2
53	4.8	2.3	1.0	1.0
54	4.1	3.2	0.9	1.3
6	4.6	2.5	0.6	0.6
7	4.0	2.1	0.8	0.7
Averages	4.8	2.7	1.6	1.3

Greenwald[55] that certain protein precipitants, notably methyl alcohol, occlude creatin and certain amino-acids, led us to start an investigation to determine, if possible, to what extent the various protein precipitants (picric acid, trichloracetic acid, metaphosphoric acid, methyl alcohol, tungstic acid [56]) occlude creatin. As yet, we have not made a sufficiently large number of determinations to draw any definite conclusions, but publish here (Table 5) a few of our results obtained from precipitating the proteins of whole blood and plasma with picric acid and metaphos-

54. Denis: Ibid. **25**:513, 1918.
55. Greenwald: Ibid. **21**:61, 1915.
56. The use of this last was suggested by Folin (personal communication).

phoric acid. The method employed was briefly as follows: About 30 c.c. of blood from an arm vein were aspirated into a small Erlenmeyer flask containing about 0.1 gm. of potassium oxalate.[57] Ten c.c. of this mixture were taken for the determination of creatin and creatinin in whole blood. The balance was centrifuged (at 2,000 revolutions per minute for 10 minutes) and the plasma pipetted off. Definite volumes of plasma and corpuscles were then taken for analysis. The corpuscles were laked by making up to a definite volume with distilled water. In a given sample the same precipitant was used for coagulating the

TABLE 5.—Comparative Values of Yield (Creatin and Creatinin) from Supernatant Liquid and Coagulated Mass. Plasma (Pl.) and Whole Blood (W. B.), Mg. Per Hundred C.c.

Method	Sample	Whole Blood			Plasma		
		Supernatant Liquid	Supernatant Liquid plus Coagulum	Percentage of Total from Supernatant	Supernatant Liquid	Supernatant Liquid plus Coagulum	Percentage of Total from Supernatant
Denis	10	6.8	7.8	82	1.1	2.5	44
	11	3.8	4.9	78	2.9	4.2	69
	6	4.2	4.5	94	2.5	2.8	89
	7	3.9	4.2	93	2.5	3.4	74
	12	4.7	5.5	86	2.2	4.0	55
	13	2.4	3.1	77	1.2	2.5	48
	14	6.6	8.5	78	1.6	3.0	53
	15	3.8	4.3	88			
	16	3.6	4.2	86			
	17	4.1	4.8	85			
	18	4.5	5.1	88			
	19	4.1	5.2	79			
Folin	20	4.6	5.1	90	2.0	3.9	67—
	21	7.0	8.4	83	3.4	4.0	85
	4	5.9	7.5	79	4.9	5.1	96
	5	5.2	6.5	80	3.8	4.4	86
	22	5.9	8.3	71	4.0	5.1	80—
	23	6.6	7.4	89	3.6	4.2	81—
	24	6.2	7.4	84			
	25	6.2	8.1	77			
	26	6.8	9.0	76			

Average percentage yields from supernatant fluid:
Denis Method: Whole blood, 84.5 per cent.; plasma, 61.7 per cent.
Folin Method: Whole blood, 81.0 per cent.; plasma, 82.5 per cent.

proteins of whole blood plasma and corpuscles. After coagulating the proteins in each, the suspension was centrifuged (2,000 revolutions per minute for 10 minutes) and the supernatant liquids were analyzed for creatin and creatinin. The coagulated masses from whole blood, plasma and corpuscles were separately washed thoroughly with five 50 c.c. portions of distilled water (further washing did not increase the yield), the washings added together and concentrated in acid (normal) solution and then analyzed for creatin plus creatinin.

The results presented in Table 5 suggest that a considerable amount, roughly 20 per cent., of the creatin of whole blood (we have figures

57. Folin: J. Biol. Chem. **17**:475, 1914.

to show that the creatinin is but little, if at all occluded) is occluded in the coagulated proteins, and that in plasma, precipitated with metaphosphoric acid, a relatively larger amount of creatin is occluded. Moreover, in a few determinations which we have made on the corpuscles (metaphosphoric acid) we have found from four to five times as much creatinin plus creatin in the coagulum as in the supernatant liquid. These results suggest that the corpuscles may contain some chromogenic substance other than creatin which, on autoclaving, gives a color with picric acid. Investigations have been started involving the addition of known quantities of creatin and creatinin to whole blood, corpuscles and plasma in the hope of throwing further light on this problem.[58]

The determinations of creatinin and creatin on whole blood and urine shown in Tables 1 and 2 were all made with picric acid precipitation. While determinations of creatin in whole blood or plasma by any of the current methods admittedly may not represent actual quantities of creatin present, nevertheless, such determinations are of value in a statistical study as showing an empirical departure from the normal. At least this is all that can be said of them until more accurate methods are introduced.[59]

SUBJECTS

The nine normal controls were volunteers from the medical corps detachment of the hospital. The cases reported were all of them hospital patients suffering from arthritis in various stages of the disease, from acute attack to well advanced convalescence. In every case (patient or normal control), the individual was put on a creatin- and creatinin-free diet for a period of three days, and on the fourth day, before breakfast the sample of blood was taken. The urine used for analysis was that obtained during the last twenty-hour hours. The diet averaged 50 gm. of protein, 65 gm. of fat and 300 gm. of carbohydrate, yielding about 2,000 calories. Only two of the cases were febrile during the period of observation (these so noted).

OBSERVATIONS ON THE RESULTS

1. In Table 1 are recorded the results of the analyses of the blood and urine of nine normal controls and fifty cases of arthritis in various stages of the disease. These cases are arranged according to ascending

58. The studies forming the basis of Tables 4 and 5 were contributed by Lieutenant Buckman alone.

59. This work was completed before the system of blood analysis by Folin and Wu was published. Folin and Wu: J. Biol. Chem. **38**:81, 1919.

values for "creatin" in whole blood. Broadly speaking, about half of these show values for blood "creatin" above the highest normal value.

2. Many of the high values for creatin in the blood seem to fall in that group of cases characterized by very acute symptoms or by a very chronic course without much change from day to day.

3. Despite the definite glucose intolerance shown by a majority of the cases (see Part III) only three of the cases show creatinuria on the diet given. This creatinuria cannot be attributed to dietary factors.

4. In three of the four instances in which creatinuria occurred, there was a distinct elevation of the creatin of the plasma, but in the fourth instance it was only 1.3 mg. per hundred c.c.

5. Two cases, one on two observations, showed very high values for creatinin in whole blood (4.6; 5.2 and 6.0 mg. per hundred c.c.) with normal values for total nonprotein nitrogen in the blood. It is remarkable that in one case in which a third creatinin determination was done, the value fell to normal simultaneously with marked clinical improvement of the patient.

6. Fully one-fourth of the cases show an abnormally low creatinin elimination, not attributable to diet (starvation). But, as Shaffer [60] pointed out, this is seen in a large variety of pathologic conditions and is not characteristic of any particular disease group.

7. About one-third of the cases did not reach the level of nitrogen elimination indicated by the diet in the three day period allowed.

8. Only two cases out of the entire series show an abnormal elevation of the total nonprotein nitrogen of the blood.

9. In Table 2 are presented ten cases. In nine of these, at least two determinations at different stages of the disease were made. Seven of these show a fall in the creatin content of the blood simultaneously with clinical improvement. Two showed the opposite. One shows no change in the creatin content of the blood, and no change clinically.

SUMMARY

1. Determinations of the creatin, creatinin, and nonprotein nitrogen of the blood and urine of forty cases of arthritis and nine normal controls are presented. About one-half of the cases of arthritis show an abnormally high value for blood creatin.

60. The average normal values for creatinin in whole blood are generally given as from 1 to 2 mg. per hundred c.c. There is a great discrepancy regarding normal average values for creatin. Hawk (Loc. Cit.) gives 3 mg. per hundred c.c. Hunter and Campbell give 5.52 (uncorrected) mg. per hundred c.c. Our own figures are somewhat lower, 4.3 mg. per hundred c.c.

2. A certain number of patients show a decline in blood creatin simultaneous with clinical improvement.

3. Only three of the cases show creatinuria.

4. Only two cases show an abnormal elevation of nonprotein nitrogen of the blood.

5. Figures are presented which suggest that a considerable amount of creatin is occluded in the precipitation of the proteins of whole blood and plasma.

STUDIES ON ARTHRITIS IN THE ARMY BASED ON FOUR HUNDRED CASES

V. ROENTGEN-RAY EVIDENCES, CLINICAL CONSIDERATIONS, TREATMENT, SUMMARY, CONCLUSIONS AND CLINICAL ABSTRACTS OF CASES STUDIED *

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ROENTGEN-RAY EVIDENCES

Roentgen-ray studies were made in all cases of the 400 in which there was any suspicion that there might be additional evidence discoverable by these means. One hundred and seventy-nine series of plates were made, ranging from one to twenty plates in any given series, and the percentage of positive findings justified omitting recourse to the roentgen ray in the absence of such suspicion.

The total number of cases of arthritis studied was 400. One hundred and forty-seven cases, or 37 per cent., were studied with the roentgen ray. Forty-six cases, or 31 per cent. of the 147, gave positive roentgen-ray findings. The forty-six cases giving positive roentgen-ray findings constituted 11½ per cent. of the whole series of 400 cases. In other words, making allowances for cases which may have been overlooked, it is clear that a relatively small number of the entire series, say less than 15 per cent., showed evidences of bony change when examined by the roentgen ray.

This is of some interest in the light of our being able to date the onset of arthritic manifestations in most cases from a certain given period, and often abruptly from a fixed date. It is not at this time possible to give the approximate duration of disease necessary in these cases for the production of bony change giving roentgen-ray evidence, but it is clear in the group studied that arthritis, and its accompanying phenomena, may exist for many months, producing gross superficial changes without resulting in evidence that the roentgen ray can detect, except in the increased shadows of the soft parts.

It is common experience in civil life that the bulk of patients presenting chronic arthritis show definite roentgen-ray evidences by the time they apply for treatment. It early became apparent, however, in

* I desire to express obligation for the helpful cooperation of Lieut. Milton C. Glover, M. C., chief of the roentgen-ray laboratory, and Lieut. William A. Newell, M. C.

this series that for purposes of determining the severity of symptoms, or presenting evidence before disability boards, negative roentgen-ray findings could not be depended on as proof that disability did not exist. It was in some cases a matter of the greatest difficulty to decide whether the patient did or did not have pain or limitation of function. Of completing our analysis of 420 cases, we came to regard roentgen-ray evidences as implying in general a marked degree of chronicity. Practically all of the advanced changes met with in civil life were reflected in this series, and certain soldiers showed the most pronounced pathologic evidences from the roentgen-ray standpoint.

The cases in which, perhaps, roentgen-ray evidence was most frequently desired but was apt to be lacking were those in which disabilities were referred to the back, including spondylitis, paravertebral myositis, sacroiliac disease, etc., in which differential diagnosis was difficult. The evidence was frequently deficient in these cases, not only because good roentgenograms of the spine are often obtained with difficulty, but because much time is required for an arthritis of the several articulating vertebral structures to exhibit pathologic processes detectable by the roentgen ray.

In making provision for the treatment of a group such as has been considered here, elaborate roentgen-ray equipment and a well experienced personnel would be essential.

CLINICAL CONSIDERATIONS

A clinical survey of the topic herewith presented develops a number of points of interest. The cases occurring under military conditions differ from those met with in civil life in respect, chiefly, of the age, the immediately exciting factors and the greater tendency to improve. It was found that nearly all types encountered in civil life were represented, although the incidence of some varieties was different. In general, the age of the individual and the relatively limited chronicity of the disease precluded the occurrence of gross lesions of the degree and frequency met in the later decades of life. It was in some part because of this limited organic change that gratifying end-results could be achieved, making this group particularly worthy of therapeutic effort. Although chronic arthritis in the young is not a rare disease, and some of the most refractory cases occur at this age, nevertheless, its frequency is vastly increased by war conditions, and this situation presented unusual opportunity for observing the problem in large numbers of men from a new angle.

Because of the lesser frequency of structural bony change, and the gross evidence thereof, it was sometimes difficult to reach decisions as to the existence or degree of disability. As mentioned under the section on roentgen-ray findings, cases involving the spine and sacro-

iliac joints presented the greatest difficulty in diagnosis. There were many instances of lowered function in bending forward, accompanied often by some pain in the lower spine, in the paravertebral regions, or in the sacroiliac joints, although outstanding and severe disabilities of this nature were not of great frequency.[1]

The minor neuroses, secondary to illness and war conditions in general, often complicated the picture. A certain number of cases showed acute tenderness to pressure at and below the costal borders posteriorly, suggesting, but not simulating, lumbago.

A small number of cases called to mind the picture presented by certain supposedly neurotic conditions, unaccompanied by organic change, in which the individual bends forward as though the subject of advanced vertebral disease (Case 48; Jansen). Under the heading "camptocormie; spondylose antalgique" and other titles, the French have directed considerable attention to this subject, and the diagnosis between it and spondylitis deformans is acknowledgedly difficult.[2] For the reasons mentioned under the preceding paragraphs and under "Roentgen-ray Evidences," the conclusion was reached that in the presence of disabilities referred to the back as a whole, it was unsafe to deduce without prolonged, exhaustive observation that organic disease was not present.

The exciting factors other than exposure, need a little comment. It is somewhat surprising that dysentery should occupy the second place. The evidence respecting this and the next most frequent exciting factor, "flu," was obtained from the service records of the men, and from a very close questioning as to their whereabout and condition at the time of the onset of the arthritis, and is hardly open to serious error. The arthritic attack came on at all stages of the apparently causative disease, but one interesting point was developed in respect of the occasional onset of rheumatic disability nearly or quite coincident with convalescence, when the conditions of life were not adequate to explain it. This point is deserving of further scrutiny, and was illustrated in about thirteen clear instances of which the following cases are typical. Only the last 150 cases, or so, were closely analyzed in this regard, but other cases seen earlier will be suggested by reference to the "Clinical Abstract of Cases Studied."

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1. A brief but comprehensive survey of back disabilities in the army is given by Sherwood and Jones (J. A. M. A. **72**:1599 [May 31] 1919). They call attention to the frequency of sacroiliac conditions, the infrequency of malingerers, and the great difficulty in reaching a correct diagnosis. This is in agreement with our experience.

2. Hall, G. W.: Camptocormia (Bent Back), J. A. M. A. **72**:547 (Feb. 22) 1919. Saliba, John: Antalgic Spinal Distortion, J. A. M. A. **72**:549 (Feb. 22) 1919.

CASES OF ARTHRITIS OCCURRING DURING CONVALESCENCE

CASE 1.—Miss T., aged 24 years, army nurse corps, contracted influenza at Camp Grant Oct. 11, 1918. She was sick for four days and after two days of convalescence, up and about, returned to duty. In about a week she developed pleurisy and went to bed for about four weeks. At this time the effusion, which was serous, had apparently been absorbed and she was allowed to get up. After three days of convalescence, up and around the ward, she suddenly developed multiple severe arthritis which still incapacitated her, with some active symptoms as well as sequelae, eight months later. Dental foci of infection were removed at Camp Grant by extraction of teeth. Another dental focus was removed May 2, 1919, at U. S. Army General Hospital No. 9, Lakewood, N. J. The tonsils were reported negative. The genito-urinary tract was not examined.

CASE 2.—Private Reap, aged 25 years, did full infantry duty in France until Sept. 27, 1918, when he was knocked down by a high explosive shell but was otherwise uninjured. Six hours later he received a perforating wound of the right leg from a machine gun bullet. He reached a base hospital four or five days later and was in bed for three weeks. A week or two later, while going around on crutches, arthritis developed, first in the knees then in the hips and shoulders. He made a full recovery in the presence of a dental focus, although for some months he was rather depressed psychically.

CASE 3.—Sergt. Herron (Case 60), aged 24 years, while doing full duty in the field artillery was operated on for a ruptured gangrenous appendix in February, 1917, followed by drainage for seventeen days. About April, 1917, after recovery, he was returned to light duty. About May 1, 1917, he first noticed aching in his hips. He had never had any previous attacks of rheumatism and could not ascribe the onset to exposure to cold or wet. In a few days, hands, fingers and knees became involved, but after running a protracted course, he was returned to full duty. In June, 1918, he contracted influenza and spent ten days in the hospital. He was then returned to full duty on outdoor work, but was not exposed to cold or wet. After two weeks he suddenly developed an arthritis in the right hip and knee. The disease spread to many other joints and in June, 1919, he was still invalided, suffering from sharp exacerbations. He had apparently had no foci of infection in the teeth, tonsils or the genito-urinary tract at the time of the onset, and no demonstrable surgical focus was discovered even after repeated examinations at U. S. Army General Hospital No. 9.

CASE 4.—Private Moore, aged 25 years, gave a history of having had rheumatism in the lower limbs for four weeks in 1915. After his recovery, two teeth were extracted. He did full duty in a machine-gun battalion. Early in October, 1918, he was gassed; this was followed by vomiting and bloody diarrhea, lasting about two weeks. He was sent to a field hospital for five days, and was then returned to full duty. A day or two after return to full duty, his diarrhea and vomiting having both ceased for a similar period, rheumatism came on in the right ankle while marching, spreading in a few days to the knee and back. He made full recovery in the presence of a probable focus in the tonsils.

CASE 5.—Lieut. Jaycox, infantry, aged 54 years, had never had a previous attack of rheumatism and did work as transport officer in the Argonne sector. In the last week of July, 1918, dysentery developed. It ceased about September 1. After this attack he returned to full duty, the diarrhea remaining in abeyance without medication. Toward the end of September he suffered for three or four days with some diffuse stiffness. October 1, he was sharply incapacitated by involvement of the right shoulder, knee, ankles and lumbar spine. This officer made a considerable but slow improvement in the presence of a tonsillar focus, removal of which was contraindicated.

CASE 6.—Private Tingue (Case 95), aged 27 years, had had rheumatism of the left knee at the age of 14. He did full duty overseas. In August, 1918, he suffered from dysentery which he says was epidemic in the division at that time. The dysentery lasted about two weeks and then practically ceased. After having had no medicine for his bowels for two or three days, and while doing full duty, both knees became swollen, confining him to bed. His hips and left shoulder became involved later. He occasionally had a return of the looseness of the intestines in the hospital, but never more than three or four times a day. He was still invalided in May, 1919, during which month a tonsillar focus was removed at U. S. Army General Hospital No. 9.

It is, of course, entirely possible, theoretically, that when exposure acted as the exciting agent in producing arthritis, it did so through the intermediation of a focus of infection by lowering the general resistance to such infection or by favoring the growth or extension of such a focus until it assumed systemic importance. It is unnecessary to assume such intermediation, however, in the instances caused by dysentery and influenza, although it may exist. The large independence as regards focal infection shown by these men during their convalescence; the abrupt onset following exposure in many cases; the absence of demonstrable foci in many; the failure of removal of foci to affect some, and other considerations, make it unsafe to assume that all cases are caused by this intermediation. It is probable that the question cannot be settled as yet, and that we must admit the possibility that exposure per se is capable of inducing "rheumatic" disability.

Very few of the 400 patients studied presented any important intercurrent conditions. Cardiac involvement was negligible, except in a few who gave clear histories of acute inflammatory rheumatism. This bears out the experience of civil life in which there is apparently complete independence of chronic arthritis and cardiac affections, although acute inflammatory rheumatism, complicated by valvular disease, may, of course, be subsequently followed by chronic arthritis. It is possible that the emphasis placed on cardiac examination in the draft largely prevented the occurrence of such types.

Although many of the cases of this series had a febrile onset, probably in only a small number was this representative of what is properly known as acute inflammatory rheumatism. A small number of cases under our observation ran an acute inflammatory course, with effusion, swelling, pain and loss of function. These patients made a rapid convalescence and sometime later, developed another attack but could not properly be classed as cases of acute inflammatory rheumatism. On several counts it seems clear that in addition to the low grade fever sometimes encountered in chronic arthritis, this disease may manifest itself in sharper outbreaks with higher fever, shorter course and no residual arthritic or cardiac pathology. It is difficult or, perhaps, impossible at present to draw a line sharply between chronic arthritis

which includes these occasional manifestations and acute inflammatory rheumatism itself, and several cases of this series appeared to merge from one condition into another.

Acute inflammatory rheumatism, and the accerbations of chronic arthritis, or even chronic arthritis itself, seem, therefore, to differ in degree rather than in kind, except that circulating bacteria may cause valvulitis, emboli and sepsis. True sustained inflammatory rheumatism with valvulitis is probably due to bacterial infection only. The acute exacerbations of chronic arthritis may apparently occur in the absence of bacterial infection and may follow other causative agents. In both conditions, however, the arthritic phenomena probably result from some common intermediary step, such, for example, as that productive of a lowered carbohydrate tolerance, secondary to focal infection or other agencies.

The present series afforded interesting data as to the unusual manifestations which the "rheumatoid" state may sometimes induce. Case 22 (Oberg) described in detail under "Dietary Considerations" and under "observations on the blood sugar," was a case in point. From the clinical standpoint, there is apparently no room for doubt that the pleuritic manifestation in the left chest occurred as an exacerbation during improvement and was referable to the underlying cause of the arthritis. Following, as it did, closely on effusion into a knee joint and being accompanied by fever of only trifling degree, and by slight signs of effusion in the chest, it was at the time regarded as being rheumatic rather than infectious or bacterial in the usual sense. The next manifestation corroborated this view. A few days later, the patient developed all the clinical signs of a mild phlebitis with very slight fever, great edema of the leg, tenderness, and a mass in the upper femoral region. This, in turn, subsided.

Another case in point was that of a man (Folden; Case 63), aged 24 years, a railroad section hand in civil life, who for ten years past had had arthritic pains, worse in bad weather, chiefly in the right leg. He had suffered intermittent disability since induction, but improved sufficiently to go "over the top" once. In the course of shifting and progressive disability in his left leg and elsewhere, and about four weeks after removal of his tonsils, which constituted the only focus, he developed apparent obstruction to the circulation of that leg, characterized by swelling, cyanosis, tenderness and enlargement of the inguinal lymphatics with tenderness over the popliteal and femoral vessels. This condition suggested phlebitis because of the great enlargement of the calf and cyanotic appearance of the whole limb, and was quite atypical of rheumatoid manifestations at large. It was apparently truly rheumatic, however, and was associated with pains at the costal border posteriorly, nearly complete loss of function of the

left arm from arthritis and myositis, and fever as high as 101 F. It is not inconceivable that we may come to regard certain inflammations of the serous membranes, such as the pleura, unaccompanied by any frankly rheumatic phenomena, as fundamentally referable to the same pathology which more frequently causes inflammation of the synovial membranes of joints and the other evidences of arthritis.

Studies of the morphology of the blood revealed little of interest. Considerable attention was directed by First Lieut. J. W. Sherril, director of the general laboratory at U. S. Army General Hospital No. 9, to the examination of blood smears, but no noteworthy departures were detected as to the types of cells encountered, platelets, or other elements of the blood morphology. The only point deserving of mention is the rather large number of differential blood counts showing a relatively low percentage of polymorphonuclears with a corresponding increase of the mononuclears. It could not be determined that this bore any relation to the severity or stage of the disease. The polymorphonuclears were 55 per cent. or less in 21 per cent. of the cases studied. They were 50 per cent. or less in 8 per cent. of the cases studied.[3] A normal or higher percentage of polymorphonuclears was a frequent concomitant of the most severe and refractory types of cases.

Twenty-eight cases, or 7 per cent. of the 400 cases analyzed, showed a leukocytosis above 11,000 and under 13,000. Twenty-eight cases, or 7 per cent. of the 400 cases analyzed, showed a leukocytosis above 13,000. Fifty-six cases, therefore, or 14 per cent. of the 400 cases analyzed, showed a leukocytosis of more than 11,000. These figures are based on the series as a whole, irrespective of types, chronicity or severity of the disease, but do not include changes due to intercurrent conditions.

Flatfoot sometimes added to the difficulty of both diagnosis and treatment, and is a factor that should be considered in any large provision for a group such as the present. The time and attention required for the proper care of this condition could not be afforded at the hospital, although some of these cases were secondary to the arthritis after long invalidism.

In the past, much attention has been given to the clinical classifications of the various types of arthritis. It is now becoming apparent that a new and simpler classification is needed. This is indicated in part by the rôle which foci of infection are known to play in arthritis at large. The data afforded by this series of cases as to the frequency with which varying types may follow exposure, dysentery or infectious

3. Owing to the closure of the hospital and the subsequent inaccessibility of many records these percentages are based on full differential blood counts in 178 cases.

diseases of almost any kind, and the common response of many of these different types of cases to several lines of therapy, is further evidence of the common origin of many of them. There are undoubtedly cases in which hypertrophy and overgrowth of bone form the outstanding evidence. There are other cases in which atrophy of cartilage and bone is the predominating factor. It is possible, however, in the majority of cases, sooner or later to demonstrate evidences of both processes, although there are types of arthritis which must, as yet, be left within classifications of their own, for example, osteitis deformans. It seems more rational, in the light of our present knowledge, to regard the usual types as referable fundamentally to the same pathologic factors, influenced in certain cases toward the production of one clinical picture and in other cases toward another.

TREATMENT

The present studies as to the nature and best treatment of arthritis in the army were undertaken with the intention of finally translating overseas, to the site where most cases develop, those methods and conditions which had been found to give the best results and reach the largest number. No attempt was made to exploit any particular kind of therapy, as it was believed that only experience along various lines with this unusual group could indicate the varieties and standards of treatment best adapted to the given conditions. This belief was borne out in a practical way.

It would seem on superficial analysis that a group of cases of chronic arthritis of the size here presented would provide experiences in the various forms of therapy applied to this disease on unusually large scales. It is true, that opportunity was afforded for carrying out any given line of treatment at some length, but as stated under "Clinical Considerations" the group here discussed presented one outstanding departure from the group of arthritics encountered in civil life, namely, in respect of the greater tendency of the soldier to improve or recover in the majority of instances, if given a fair chance. A large number of patients were recovering on admission or had recovered following nothing more fundamental than rest and external measures, notwithstanding severe and protracted invalidism. This fact, together with our own experiences, forced on us consideration of the results obtained by the expectant plan of treatment when based on such measures as baking, massage, hydrotherapy, electricity and the like. These had consequences much more encouraging than are encountered in civil life, and led us to postpone certain more radical types of treatment until they were clearly indicated. It became obvious that for the group, as a whole, the importance of the above external measures, as adjuvants, at least, would have to be recognized, although this conclusion did not

apply to the most severe cases and cases of longest duration in the same degree. By and large, this group, as a whole, constituted an unintended experiment on a large scale in the artificial induction, through the hardships of warfare, of rheumatic affections in young men of an age least frequently attacked by them.

It must be clearly emphasized, however, that the kinds of treatment which received greatest emphasis were, first, those based on attempts to discover and remove foci of infection when present, and second, those based on local and external measures. Other forms of therapy figured less conspicuously. As mentioned elsewhere, every case presenting on the service was thoroughly analyzed by the ear, eye, nose and throat department, the genito-urinary department and the dental department for evidences of focal infection, irrespective of whether the patient presented active symptoms or was entirely cured of the disease for which he was invalided. This was, of course, additional to a complete routine physical examination, including blood counts, Wassermann test, etc., made on admission. The analysis for foci and the action based thereon were the premise from which all other therapy started, and anything else undertaken was additional to the principle of removing causative surgical pathologic conditions. Additional therapy was instituted either pending improvement from this source or after efforts along these lines had failed. The position was taken that it was philosophically unsound to attempt to treat these patients by other means in the presence of removable and potentially causative surgical processes. There were, of course, many instances in which the existence of a surgical lesion or its relation to the disease were in question, but wherever possible, the soldier was given the benefit of the doubt. The exceptions to this rule were made in those cases in which operative procedure was contraindicated, or where, after recovery, such procedure was refused by the soldier. In practically every case in which the disease was stationary, growing worse or improving unsatisfactorily, operative removal was carried out. In the case of soldiers who had made an essentially complete recovery on admission, such action was made optional.

As will be seen in the statistical analysis, the tonsils formed the most frequent site of focal infection, and it would seem, from our experience with this large group, that the emphasis placed on these tissues in their relation to arthritis is, in general, justified. Two hundred and eight patients had foci in the tonsils, which is 52 per cent. of the entire series and 71 per cent. of those showing foci.

Thirty-four patients, or 8½ per cent., recovered after the removal of foci. Thirty-one patients, or 7¾ per cent., improved after the removal of foci, but the end-result may have been favorable in certain unimproved cases which disappeared early from observation.

The varying opinions held by even experienced observers as to the existence of disease in the tonsils, the results of culture and section of the tonsils after removal, and the results of tonsillectomy itself, have emphasized the fact already indicated by others, that it is difficult or impossible to be sure that tonsillar infection does not exist, except after thorough enucleation. Only those most experienced in weighing this point are likely to advance a sound opinion in doubtful cases, and even they may err on either side. A detailed consideration of this and other points regarding the relation of tonsillar infection to arthritis has been well brought out in a recent article by Lillie and Lyons.[4] The evidence adduced by a large number of cases in this series has clearly indicated, as pointed out, an impressive independence of focal infections at large, on the part of arthritics at this age as compared with older subjects. On the other hand, it must be granted that the conservative step in a refractory case is the removal of focal infection, and the apparent normality of the tonsillar tissues at the hands of any observer is not unfailing evidence that the tonsils are not acting as focal agents. It is difficult to steer a mean between these extremes. It is probable that for practical purposes it is wiser to regard the relative independence of focal infections shown by these young subjects as an academic consideration, and to regard possible foci of infection as causative agents until proven otherwise.

In thirty-four cases a culture study was made for *Streptococcus hemolyticus* following tonsillectomy. Twenty-one cases, or 62 per cent., were positive for *hemolyticus,* and thirteen cases, or 38 per cent., were negative for this organism.

The removal of dental foci played an important rôle also, although our figures show that dental foci were represented in fewer numbers; namely, 33 per cent. of all cases, in contrast with 52 per cent. of all cases showing tonsillar foci. It seems fair to say, that clinical observation substantiates the relative importance indicated by these percentages. Improvement may be marked after attention to either, but was rather more striking in the series in relation to tonsillectomy. This may easily be explained by the fact that dental foci, unless multiple, are actually smaller.

Our figures show that genito-urinary disease afforded only a small percentage of the foci met with, and, from the clinical standpoint, in only about two of the last 150 cases studied could such infection be found to bear any real relation to the arthritis. There is, therefore, relatively little necessity to emphasize treatment of genito-urinary conditions as part of the treatment of arthritis as a whole among soldiers,

4. J. A. M. A. **72**:1214 (April 26) 1919.

a consideration which would have importance in making provision for the care of larger numbers of arthritics, were the war still in progress.[5]

NONSPECIFIC PROTEIN INJECTIONS

It was demonstrated twenty-five years ago that the course of typhoid fever could be influenced favorably by the subcutaneous injection of killed typhoid organisms, or even pyocyaneus bacilli in the form of a vaccine. Since then other pathologic conditions have been treated by vaccines on this principle, but only within the past five or six years has it been appreciated that the beneficial effects following the injection of foreign protein may be the results of a nonspecific immunologic reaction. Miller and Lusk [6] first suggested the treatment of arthritis by means of nonspecific protein injections and definite benefit is known to follow these measures in certain types and proportions of cases of arthritis at large, but the method, as a whole, is in its infancy, and its basis of action is as yet a matter for speculation.[7] It is generally agreed that this form of therapy, as applied to arthritis, achieves its best results in the acute forms; subacute and chronic arthritis responding less readily, in the order indicated. The cases in the present series to which this treatment was given belonged, for the most part, in the chronic category, for the reasons elsewhere mentioned, and opportunity to use the treatment where benefit was most likely to result was infrequent. The method is generally regarded as being free from danger, but Thomas [8] has reported several untoward results, and the work of Longcope suggests the possibility of producing nephritic lesions by repeated protein intoxication.[9] The reactions which accompany treatment along these lines are generally unpleasant, and Snyder has reported gastric hemorrhages and mild hematemesis. Cole, and Miller and Lusk, have cautioned against the indiscriminate use of these measures, and Jobling has emphasized the dangers which may follow large injections. Opinions differ as to the size of the doses to be administered, and Snyder advises beginning with small doses of from five to ten millions. Miller advises beginning with seventy-five millions [9a] and in a recent comprehensive study of the changes in the blood

5. I am indebted to Capt. George G. Smith, M. C., U. S. Army, chief of the genito-urinary service at U. S. Army General Hospital No. 9, for his helpful analysis of this phase of the subject.

6. J. A. M. A. **66**:1756 (June 3) 1916.

7. A bibliography will be found in "Clinical Report of Nonspecific Protein Therapy in the Treatment of Arthritis," by R. G. Snyder: Arch. Int. Med. **22**:240 (Aug.) 1918.

8. J. A. M. A. **69**:770 (Sept. 8) 1917.

9. J. Exper. M. **18**:678, 1913.

9a. Personal communication.

following such therapy in ten cases of arthritis, Cowie and Calhoun [10] used doses of one billion without any reported ill effects.

In view of the conditions, however, under which the subjects of the present study arose, it was believed safer and wiser to begin with a low average figure. The army typhoid vaccine was accordingly used in an initial dose of twenty-five million, the second dose, when given, being fifty million and the third, seventy-five million. Nineteen patients received nonspecific protein injections in a vein of the arm.* Of these, seven were definitely improved, ten were unimproved and in two the results were uncertain. Of the seven improved, two were apparently cured, and of those unimproved, one patient was apparently made worse. Some of the patients receiving protein injections desired a second and even a third dose. This was true in one case in which great benefit followed the treatment, and in another in which only slight benefit accrued. A rather larger number of patients refused a second injection and nearly all the patients suffered a pretty severe subjective reaction. In slightly more than one-half of the instances, the temperature rose to almost a uniform height, from 103 to 104 F.

Ten of these cases were followed in respect of the blood count.[11] In the first seven cases, the full blood counts and differentials were made by Lieut. Leslie N. Gay, M. C., to whom obligation is expressed for the care exercised. The remainder were made under the critical direction of Lieut. J. W. Sherrill, M. C., director of the general laboratory, U. S. Army General Hospital No. 9. A full and differential blood count was made immediately before the injection, during the height of the reaction, and again twenty-four hours later. In a few instances, a count was made shortly after the injection, before the reaction had achieved its maximum. This series showed the usual picture of an initial leukopenia followed by a sharp leukocytosis, during the reaction, which averaged 16,470 leukocytes. The degree of leukocytosis apparently bore no relation to the leukocyte count before injection. Twenty-four hours after the injection, or after the subsidence of fever, the leukocyte count showed no important change from its original level, in four cases being slightly lower and in seven cases slightly higher. One patient had a leukocytosis of 11,400 during the reaction, and a delayed rise up to 30,000 twenty-four hours after the initial dose, although the fever had reached its height of 102.5 F. four hours after injection. Forty-eight hours after injection the leukocytes were practically at their former level. One patient in this series showed no leukocytosis either during the reaction or twenty-four hours later after dosage of twenty-five million organisms.

10. Arch. Int. Med. **23**:69 (Jan.) 1919.
11. To save space the tables are omitted.
* Mostly with the collaboration of Capt. Louis A. Levison, M. C. U. S. A.

In general, the series showed an absolute as well as a relative rise in the polymorphonuclears and a corresponding fall in the small lymphocytes. In one case, at the height of reaction, eight hours after inoculation, the differential count showed a decrease in the percentage of small lymphocytes compared with the formula before injection, and twenty-four hours after injection the differential count showed a marked decrease in the small lymphocytes but a great increase in the large lymphocytes.

Blood counts in this series, as a whole, showed, therefore, correspondence with the usual experience in this regard. In none of the smears examined were any pathologic cells seen, and both platelets and red cells were apparently normal. This is at variance, as far as it goes, with the carefully studied series of ten cases reported by Cowie and Calhoun,[12] who describe many kinds of atypical cells, but this difference may be due to the very much larger dose of typhoid vaccine which they employed, one billion as compared with an initial dose of twenty-five million, and to the fact that they made hourly counts.

It is important and interesting to note that although nonspecific protein injections in the form of typhoid vaccine are of some benefit, within limits, on diffuse groups of arthritic cases, particularly the acute and subacute, the subcutaneous injections, as practiced routinely in the army camps on the incoming draft, have been without effect to prevent rheumatoid disabilities. Inasmuch as these subcutaneous injections were always at least three in number, and inasmuch as the febrile rise and malaise following them are common experiences, it seems that there must take place, at least in a modified degree, some of the systemic reaction which follows intravenous therapeutic injections. Furthermore, owing to loss of records or other causes, forty-six patients had received more than the regulation three doses of prophylactic typhoid injections (11.5 per cent. of the whole series); some men received as many as fifteen injections of the typhoid vaccine during their recent army service prior to the onset of the arthritis. It seems reasonable to deduce, therefore, that there is no prophylactic effect as regards arthritis from nonspecific protein administered subcutaneously, even after repeated dosage.

The rationale of nonspecific protein injection, when followed by beneficial results, has never been explained. It is well known to critical students of arthritis, that agents which profoundly disturb the existing conditions of life, such as the roentgen ray, radium, probably thyroid extract, and even such factors as excitement, a fatiguing journey, etc.,

12. Loc. cit.

may be followed by periods of benefit. Some of these agents, at least, are known to stimulate the body metabolism as a whole and to induce increased catabolism.

It is also clear that a lowered intake of food may be followed by unquestioned benefit in a definite proportion of cases. This is graphically exemplified at times, as in several cases of this series (Case 53, Mrs. K.; Case 52, Lynch; see "Dietary Consideration" and "Clinical Abstract of Cases Studied"), by the period of enforced starvation following such operations as tonsillectomy, or abdominal section. Under these conditions, catabolism runs ahead of anabolism and the body draws on its store of glycogen. The difficulty in the utilization of carbohydrate by the arthritic has been sufficiently developed in the chapters on "Blood Sugar" and "Dietary Considerations." There is other evidence to indicate that carbohydrate is caught up in some important way in the pathology of this disease.[13]

Barr and DuBois [14] have shown that the respiratory quotients during the chill of malaria suggest rapid combustion of glycogen stores during the violent muscular exercise of shivering. Attention has been drawn by Cowie and Calhoun to the fact that the characteristic malarial chill is probably an example of protein intoxication and reaction. There is every reason to believe that the same rapid combustion of glycogen takes place during a severe reaction from nonspecific protein. In view of the evidence grouped under these heads, it seems possible that the benefits from protein injection in arthritis may, in part, result from the heightened metabolism accompanying the marked febrile rise with consequent combustion of available carbohydrate. A factor contributory to this may be the incidental low food intake which accompanies the usual malaise of twenty-four hours or more. That this is the whole explanation can hardly be believed; that it supplies some of the contributory factors seems probable.

DIETARY CONSIDERATIONS

Experience in civil life with refractory forms of arthritis, has indicated a definite relationship in certain types of cases between the intake of food, on the one hand, and the incidence and perpetuation of the symptoms of chronic arthritis on the other. This relationship can best be illustrated by the fact that in certain cases of arthritis, not amenable to other therapy, the patient can be influenced greatly for the better or relieved of all symptoms by a sharp curtailment of the food intake as a

13. See section on Creatin; also, Pemberton, R.: Am. J. M. Sc. **43**:678 (May) 1917.

14. Arch. Int. Med. **21**:627 (May) 1918.

whole. Such a reduction can for purposes of discussion be considered in terms of the total calories involved, but evidence at hand has indicated that the carbohydrates may be the most concerned of the three foodstuffs. It is not intended to set forth here the observations forming the basis for this conclusion, as these have been elsewhere reported.[13] Experience in this connection, however, formed one of the influencing factors in determining the lines of attack on the present problem as a whole, and afforded one of the several lines of therapy undertaken in this series. Several instances will be cited in detail because of the further evidence they afford of the practicability of these methods, and of certain other points of interest relating to the nature of the present problem. As mentioned under the opening paragraphs on "Treatment," the number of patients treated by dietary means was smaller than the number of arthritics in this series would suggest, a priori, as available to any measure. The factors which made for other and simpler forms of treatment for this group, however, have been emphasized sufficiently. It has been pointed out in previous contributions, that treatment by these dietary measures should be reserved almost exclusively for those cases which are demonstrably not caused by infectious foci, cases in which the removal of foci is contraindicated, cases not accompanied by undernutrition, anemia, etc., and, in short, for that group of cases in suitable condition which has failed to respond to other measures. The evidence indicates that therapy along this line achieves its result primarily more by catering to a weakened function, than by removing the cause of that weakened function, although in the end that function may by these means be improved or restored to normal. It is, therefore, essentially an unsound policy to attempt relief of symptoms by dietary control in the presence of the demonstrably removable cause of these symptoms. Apart from this, dietary procedures of whatever kind, and particularly in the present connection, involve much cooperation on the part of the patient and considerable time, for which reason, even under the condition of civil life when patients are often willing to make any and all sacrifices to obtain relief, this form of therapy is to be employed only after full consideration. On first analysis it would appear that the conditions of a military hospital would insure control of the patients, with consequent cooperation from them far in excess of what might be expected in civil institutions, but experience has shown that this is not the case, except in respect of clearcut objective procedures, such as operations and the like which can be carried out with the efficiency of a military command. The youth of most of the patients, the shorter duration of the disease, the fact that these subjects had not suffered invalidism to

that degree which makes them willing to undergo protracted sacrifice, the loss of morale resulting progressively from treatments in many hospitals on their way back from the front, with small resulting benefit, all added cogency to the reasons mentioned for withholding these measures until clearly indicated. There can be no doubt, however, of the results achieved in this series in some selected cases and the application of these measures to the problem in hand can probably be best illustrated by a recital of a few of them, following this with a consideration of the points developed and a general discussion.

The undesirability of approaching the whole topic from too academic a standpoint, and of adding to the number of hospital days, was kept constantly before us. In carrying out the dietary measures here recorded, the effort was made to obtain results in the quickest manner, although it was appreciated that the opportunity for interesting contrasts in results was often thereby renounced. Thus, it will be noticed in the diets administered on the principle of a lowered intake, that not only were the calories reduced, but the proportions of the foodstuffs believed to be most advantageous were provided, notwithstanding that further data are desirable on the rôle played by the three foodstuffs uninfluenced by conditions of low feeding as a whole.

CASE 1.—Robbins, aged 25 years, a lieutenant in the infantry, had suffered from an attack of inflammatory rheumatism nine years previously. After experiencing some disability in one shoulder for more than two months, apparently induced by bayonet drill, he was admitted with a painful and swollen left ankle to the base hospital at Camp Lee whence he was transferred to U. S. Army General Hospital No. 9. Capt. W. W. Gailey, Jr., chief of the nose and throat department at U. S. Army General Hospital No. 9, reported that he did not think it possible that the tonsils could serve as foci of infection. Therefore, they were not removed and examination of the sinuses, teeth and genito-urinary tract proved conclusively negative. The patient had taken at one time as much as 90 grains of acetylsalicylic acid per day without relief. He was seen November 24 in consultation with Lieut.-Col. J. C. Gittings, chief of the medical service, and the conclusion was reached that he was not improving, but it was decided to wait another week in order to make sure of this. December 3 it was agreed that more active steps should be taken and he was placed on a diet. It was also agreed that any change noted could properly be ascribed to the new régime established.

Observations of the food intake of this officer for a period of about a week showed that he was ingesting an average of about 3,750 calories per day, which included about 700 calories from candy, of which he was very fond. Of this food intake about 12 per cent. came from protein, about 29 per cent. came from fat and about 50 per cent. came from carbohydrate.[14]

14. As mentioned in previous publications, it has been found convenient to estimate food values by reference to "Food Values," Edwin A. Locke, and except where the data for any given foodstuffs could not be found, these tables were used by the dieticians in charge of food estimated or prepared on the arthritic service.

December 3, he was placed on a diet of 2,051 calories, of which about 10 per cent. came from protein, 52 per cent. came from fat and 38 per cent. came from carbohydrate.

		Calories
BREAKFAST		
1 apple	150 gm.	72
1 egg	50 gm.	83
Bread	60 gm.	162
Butter	15 gm.	120
Sugar	20 gm.	80
Milk	60 c.c.	39
Coffee		
LUNCH		
Bouillon	180 c.c.	
Lettuce	40 gm.	
Mayonnaise	1 t'blespo'n	187
String beans	100 gm.	17
Bread	30 gm.	80
Butter	10 gm.	80
Orange	250 gm.	95
1 egg	50 gm.	83
SUPPER		
Steak	50 gm.	143
Bread	60 gm.	160
Butter	15 gm.	120
Tea		
Sugar	20 gm.	80
Milk	60 c.c.	39
Beets	100 gm.	40
Lettuce	40 gm.	
French dressing	2 t'blespo'n	298
1 apple	150 gm.	72
Total calories		2,051 [15]

Four days later he could move around without crutches, having been practically bed-ridden before. After eleven days the improvement was marked and he had no conspicuous ache in the hip, shoulder or elsewhere, the residual points of tenderness being few.

After this abrupt change in his condition there followed a gradual and progressive betterment. Except for occasional fluctuations, which grew fewer in number and less severe, and changes in the distribution of involvement, this case showed, as do most cases which improve along these lines, amelioration of the original picture until few and finally no joints were involved. This officer lost 10 pounds in weight and finally reached an equilibrium. His food intake was then increased by one egg, and finally by olive oil to bring his calories up to about 2,500, of which about 8 per cent. came from protein, 62 per cent. came from fat and 30 per cent. came from carbohydrate. At this point he was playing golf and walking about seven miles a day in apparently

15. It is to be appreciated that trifling differences occur in the caloric values quoted for various articles of food, according to the table from which these values are obtained. It will, therefore, sometimes happen that there may be an apparent discrepancy of a few calories between the numbers indicated in the text and the summation of the detailed diets, but these are within the inevitable error in the administration of mixed foodstuffs at large.

perfect health. Because of his desire to insure maintenance of his improvement, he was allowed to remain at the hospital until May, having by that time been essentially well for two months, so that opportunity was afforded to observe not only the original improvement but also its establishment.

The sugar tolerance displayed by this patient on four occasions is illustrated by the two composite curves on Chart 9 (page 268). The first two curves were taken during ill health and showed a definite, although moderate elevation; the last two curves were obtained during convalescence and good health, respectively, and gave essentially normal values. They illustrate that the sugar tolerance may return to normal, coincident with improvement of the individual by restriction of diet. Observations were also conducted on the basal metabolism and blood and urinary creatin and creatinin of this subject.

In contrast to this case is the following:

Case 2.—Sergt. Lowe (Case 14), aged 42 years, had been invalided for two years from progressive polyarthritis, involving all joints, without any considerable limitations in their range of motion, if cautiously and slowly carried out. This case was apparently of the so-called dry or fibrous type, characterized by few roentgen-ray changes even after a long period, although these were demonstrable along the phalanges of the hands. This soldier had had no less than thirteen different kinds of therapy without avail.[16] His food intake averaged about 2,459 calories, but after sharp reduction of his diet in varying degrees for twelve days apparently no benefit accrued, and efforts along this line were discontinued.

What might have happened had a restricted diet been longer administered cannot be stated, but experience with other refractory cases of this series at least suggests that a combination of treatment on this basis, supplemented by other measures, might have yielded more favorable results. One of the lessons learned from this series is that combinations of treatment will sometimes effect improvements, if a favorable basis be established first, when single lines of effort fail, as is shown by Case 3.

Case 3.—Sergt. Hayes (Case 6), aged 29 years, was invalided for two years. He presented widespread deformity of the phalanges of both hands with periarticular soft tissue involvement, ankylosis of the right wrist, great tenderness, boggyness, swelling and redness of the left wrist. At the outset there had been involvement of the feet, but this had disappeared. The teeth and genitourinary tract were entirely negative. A tonsillectomy was performed December, 1918. Eight weeks later there was no improvement to be detected. It was then decided to place him on a restricted intake of food. Observation of this soldier's ingestion of food for eleven days gave an average intake per diem of 3,000 calories, of which about 15 per cent. came from protein, 39 per cent. from fat and 46 per cent. from carbohydrate. He was then placed on a diet of 2,051 calories, of which about 8.5 per cent. came from protein, 50 per cent. came from fat and 41.5 per cent. came from carbohydrate, beginning January 11.

16. See appendix of case histories.

		Calories
BREAKFAST		
1 apple	150 gm.	72
1 egg	50 gm.	83
Bread	30 gm.	81
Butter	15 gm.	120
Milk	60 c.c.	40
Sugar	20 gm.	80
Coffee		
LUNCH		
Bouillon	180 c.c.	
1 egg	50 gm.	83
String beans	100 gm.	17
Lettuce	40 gm.	
Mayonnaise	1 tablespoon	187
Bread	30 gm.	81
Butter	10 gm.	80
Orange	250 gm.	96
SUPPER		
Steak	50 gm.	143
Beets	100 gm.	40
Lettuce	40 gm.	
French dressing	2 tablespoons	296
Oil	1½ tablespoons	161
Bread	30 gm.	80
Butter	15 gm.	120
Sugar	20 gm.	80
Milk	60 c.c.	40
1 apple	150 gm.	72
Total calories		2,052

Twelve days later there was unquestionably less tenderness and swelling and probably greater freedom of movement in the left wrist than at any time during the two months of observation, and there had also been for nine days distinctly less aching, of which there was at times entire absence. This improvement was noted by many observers, and was maintained with some further improvement until February 2. About this time his condition became stationary after an improvement of about 50 per cent., and remained so for some weeks under the same conditions. In this period he had been made to lead a very quiet life and had lost about 3½ pounds in weight. In the effort to hasten progress, he was given two days of sharp fasting (March 7 and 8) on 857 calories without appreciable results. This period was started by a dose of calomel which upset him considerably and may, in some degree, have complicated the issue. After subsidence of his gastro-intestinal disturbance, he was given unrestricted diet until March 23 when he was placed on about 1,400 calories, plus potassium iodid, 5 grains, three times daily, cod liver oil emulsion, 50 per cent., 8 c.c. three times daily.

No further benefit resulted from this by April 4, although the improvement was well maintained. He was then put on a full diet for three days, and on April 9 he was again placed on the original diet of 2,050 calories, plus cod liver oil and potassium iodid. To this régime a daily sweat of fifteen minutes in a hot pack was added. After about two weeks the hot pack was substituted by a whirlpool bath, with water at about 100 F. for the left arm and this was also productive of profuse general perspiration. The swelling undoubtedly greatly subsided in the left wrist and he confessed to feeling much less tender on palpation. May 8, under maintenance of this régime, the left wrist had assumed a practically normal appearance and his condition could conservatively be estimated as improved at least 90 per cent.

This case illustrates that after the institution of a reduced diet with evidence of progress as a result of the removal of a "metabolic load," the patient's condition may then remain in statu quo, but that other agencies acting on such a basis may then suffice to influence greatly the residual arthritis, although unequal to this end alone.

Case 4.—Miss H., army nurse corps, was taken sick overseas in January, 1919, and invalided home with pain, supposedly of sciatic nature, on the right side, marked disability of the left shoulder and some disability of the right hand. She was admitted to the hospital January 25, complaining of the above symptoms, and mostly of aching at night. Examination of her teeth, nose and throat revealed no surgical foci, the tonsils being particularly inconspicuous and apparently innocuous. No gynecologic examination was made. In view of her previous robust health and hard work in the army hospitals, it was believed that rest would relieve her symptoms, but after two months, during which she had had a sick leave, she was worse than on admission, and it was decided to place her on a limited diet.

Estimation of her food intake for a few days revealed that she was eating at least an average of 2,000 calories, about 17.5 per cent. of which came from protein, about 40 per cent. came from fat and about 43 per cent. came from carbohydrate. As she was fond of eating between meals, however, it is probable that her intake occasionally went above this point. In view of these figures, however, April 18 she was placed on the following fixed diet of approximately 1,700 calories, distributed as follows: 10 per cent. from protein, 62 per cent. from fat, and 28 per cent. from carbohydrate.

		Calories
BREAKFAST		
1 orange	250 gm.	96
2 eggs	100 gm.	166
Bread	30 gm.	81
Butter	15 gm.	120
Coffee		
Milk	60 c.c.	40
LUNCH		
Bouillon	180 c.c.	
Lettuce		
Mayonnaise	1 tablespoon	187
String beans	100 gm.	17
1 apple	150 gm.	72
Bread	30 gm.	81
Butter	10 gm.	80
SUPPER		
Steak	50 gm.	145
Bread	30 gm.	81
Butter	15 gm.	80
Carrots	100 gm.	18
Lettuce		
French dressing	2 tablespoons	295
1 orange	250 gm.	96
Milk	60 c.c.	40
Tea		
Bouillon	180 c.c.	
Total calories		1,694

April 23, she said that she felt better than at any time since admission to the hospital and her knees and hips were free from pain. April 24, cod liver oil emulsion, 50 per cent., U. S. P., 8 c.c. three times daily, was added. Progress was steady until May 4, when she suffered an exacerbation coincident with a protracted period of wet weather, which affected many arthritics on the service. Despite this, function apparently improved because May 13, her arm could be raised higher than at any time to date, almost vertically, and toward the end of the month she left the hospital having lost about 1 pound in weight, feeling not at all weak, able to walk three or four miles at a time, and, by her own statement as well as by the objective evidence of function in her left shoulder, substantially improved.

It is to be noted in this case, as in others previously reported, that weight was essentially maintained and that activity was possible on a caloric intake which would generally be regarded as only slightly above the minimum figure for such conditions. This patient was of large and solid build, without being fat, and she experienced little or no difficulty from her limited intake other than being deprived of the pleasures of the table. People differ considerably in respect of the way in which they tolerate a diet restricted to this degree, not only from the mental, but also from the physical standpoint. It was possible in this case to maintain this level successfully and easily, whereas with certain soldiers such a régime proved to be difficult or impossible. This patient was instructed to maintain conditions as they were for two months and then slowly to add to her intake, little by little, according to a schedule given her, as explained in previous contributions.

Case 5.—Lieut. Lynch (Case 52), aged 33 years, had had one previous attack of arthritis and was admitted to the hospital after about six months of invalidism affecting the spine, knees and particularly the feet and heels, which were swollen and extremely tender at the insertions of the Achilles tendons. Some limited benefit had followed removal of an abscessed tooth, but five months later no further improvement had taken place. Tonsillectomy was performed April 5 on general principles, although no other indications were seen by several observers, and the tonsils proved negative for *Streptococcus hemolyticus*. The experience of this patient on the two days following the tonsillectomy, during which he felt a marked improvement, coincided with observations frequently made and published elsewhere,[17] that during the postoperative period of incidental low feeding or starvation there often ensues a noteworthy improvement of rheumatoid symptoms. Following the two days mentioned, this officer grew progressively stiff and painful in respect of his joints, and five or six days after the operation was feeling as badly as before. This experience brought prominently into consideration the probable influence of diet in this particular case, and on consultation with Lieut.-Col. J. C. Gittings, chief of the medical service, it was decided to give him the benefit of the doubt. It was further agreed that any sharp change resulting from a dietary régime could properly be ascribed to it.

An estimation of his average intake of food showed that it approximated about 2,600 calories per diem, of which roughly 9 per cent. came from protein,

17. Pemberton, R.: Am. J. M. Sc. **43**:678 (May) 1917.

41 per cent. from fat and 50 per cent. from carbohydrate. Accordingly, on April 16 he was given one day of sharp fasting, his only food consisting of bouillon, coffee and bran biscuits. April 19 he was placed on the following diet of 1,641 calories, of which about 10 per cent. came from protein, 62 per cent. from fat and 28 per cent. from carbohydrate.

		Calories
BREAKFAST		
1 orange	250 gm.	96
2 eggs	94 gm.	156
Bread	30 gm.	81
Butter	15 gm.	120
Coffee		
LUNCH		
Lettuce	40 gm.	
Mayonnaise	1 tablespoon	187
String beans	100 gm.	17
1 apple	150 gm.	72
Bread	30 gm.	81
Butter	10 gm.	80
SUPPER		
Beefsteak	50 gm.	143
Bread	30 gm.	81
Butter	15 gm.	120
Carrots	100 gm.	18
Clear bouillon	180 c.c.	
Lettuce	40 gm.	
French dressing	2 tablespoons	296
1 orange	250 gm.	96
Total calories		1,641

April 20 there was less tenderness under the Achilles tendons of both feet and progress was fairly consistent from that date. About April 24 he developed a rheumatic iridocyclitis of the left eye. On this date he could walk in his bare feet and even rise on his toes, which he could not do before the diet was instituted. He could walk quite freely in his shoes and made all movements more easily. He said that he had not made so much progress at any previous time during a comparable period. The iritis ran a painful course of about ten days, exacerbations of pain being occasionally controlled by acetylsalicylic acid. April 24, cod liver oil, U. S. P. emulsion 50 per cent., 8 c.c., three times daily, was started.

The end-result in this case was that the iritis subsided entirely and he evidenced an improvement in his rheumatoid symptoms subjectively and objectively. The ocular pain had for a day or two prevented his eating, to compensate for which he was placed for two days on an unrestricted house diet, after which, with the patient's willing cooperation, he returned to the restricted diet of 1,641 calories.

This officer had of necessity led a very inactive life while on this low food intake and lost no weight. He disappeared from observation owing to the closure of the hospital, but the therapeutic benefits indicated during the period described could not be ignored.

It is of interest to note that in another less severe case on the arthritic service not under dietary treatment, the patient suffered an equally severe iridocyclitis of one eye during practically the same

period. Within about the same month, four other cases of apparently rheumatic iridocyclitis also presented in the institution among patients on other services.

CASE 6.—Private Oberg (Case 22), aged 24 years, had had at least six previous attacks of diffuse severe arthritis dating from early childhood. At the time of enlistment in the medical corps, March 18, he was a premedical student and was accepted for full duty. During training he experienced some trifling stiffness which disappeared, and he performed full duty overseas in a base hospital until the end of August, 1918, when he went to bed with fever, great pain and limitation of function in his hips and left shoulder, being unable to walk. The onset had been gradual, extending over some weeks, and from the date mentioned there was no important change in his condition until he was admitted as a litter case to General Hospital No. 9, Jan. 21, 1919, after being five months on his back.

He presented complete fixation of both knees and markedly lowered function of the left shoulder, accompanied by roentgen-ray evidences of marked erosion of the greater tuberosity of the left humerus and atrophic arthritis of the knee. During his invalidism overseas, he had received without benefit, antistreptococcus serum in September, 1918, as a therapeutic measure in lieu of nonspecific protein in the form of typhoid vaccine. He had apparently a rather severe reaction, with fever, chills and increased pain. He stated that he had also had in civilian life, during an attack, an injection of a "rheumatic serum" without benefit. On admission, he was slightly better than he had been two months previously, but the difference was trifling and his incapacity was complete.

Examination of the genito-urinary tract was negative. Roentgen-ray examination of the teeth showed one small apical abscess, and there was division of opinion as to whether or not his tonsils were entirely innocuous or whether they were diseased and constituted a possible focus. The apical abscess was removed without apparent influence. Because of the ankylosis of the hips and spine, the consequent difficulty of tonsillectomy in this case, the doubt as to the existence of tonsillar infection, and the fact that it was believed that a radical effort was justified in the attempt to avoid fibrous or bony union in the hips and knees, this soldier was placed on a rigid régime.[18]

On the evening of February 26, he was given a small dose of calomel followed the next morning by one dram of Rochelle salts. During February 27, 28 and March 1 and until noon of March 2, he was placed under conditions of essential starvation, being allowed nothing more than bouillon, black coffee and bran biscuits. February 28, consultation with Major Cleary revealed that there was a small amount of increased motion of the thighs and of the knees, with apparently somewhat less pain. For the first time in the observation of Major Cleary and myself, there was rotation of the left thigh on the pelvis. February 30, he was given 857 calories per day made up as follows:

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18. This case was followed closely by Major E. W. Cleary, head of the orthopedic department and later chief of the surgical service at U. S. Army General Hospital No. 9. His dispassionate and cordial assistance was of great value throughout the course of these studies particularly in connection with this case. It was only through the cooperation of Major Cleary and his assistants that analysis could be attempted successfully of the many complicated cases of sacroiliac, vertebral and diffuse lumbar disability which presented. It is a pleasure also to record the cooperation afforded by the other officers of the orthopedic service on the many occasions where patients were transferred or jointly treated by both departments.

BREAKFAST		Calories
1 egg	50 gm.	83
Butter	15 gm.	120
Bread	15 gm.	40
Coffee		
11 a. m., black coffee		
LUNCH		
Bouillon	180 c.c.	
Lettuce	30 gm.	
French dressing	1 tablespoon	148
Bran biscuit		
Cabbage	50 gm.	3
3 p. m., black coffe		
SUPPER		
Bouillon	180 c.c.	
1 egg	50 gm.	83
Bread	15 gm.	40
Butter	15 gm.	120
Lettuce	30 gm.	
French dressing	1 tablespoon	148
1 apple	150 gm.	72
Total calories		857

March 6, Major Cleary demonstrated that both thighs could be flexed on the pelvis to about thirteen inches from the bed, with rotation of both hips, internal and external. The right knee could be flexed relatively freely, and flexion of the left knee was increased. March 7, the acetone reaction was distinct, but not great in both urine and blood plasma; the blood carbon dioxid was 50, and he evidently had a mild acidosis.

March 8 the diet was increased by one egg and 10 gm. of butter, 163 calories in all, making a total of 1,020 calories. March 11, the patient was stood on his feet with the assistance of Major Cleary, placing his whole weight on his legs and standing upright except for the kyphosis. He moved the legs slightly as in walking and rocked the body to and fro without pain. The opinion was reached that the acute process was subsiding and that the present limitation and disability were residual. In view of the improvement and existence of a moderate acidosis, it was decided to increase the diet largely in preparation for another period of low feeding. He was placed on an unrestricted diet, which yielded about 2,700 calories, for twenty-four hours, after which, March 13, at supper he was placed on a diet yielding 1,534 calories made up as follows:

BREAKFAST		Calories
Coffee		
1 egg	50 gm.	83
Bread	30 gm.	41
Butter	20 gm.	160
1 apple	150 gm.	72
LUNCH		
Bouillon	180 c.c.	
Lettuce	30 gm.	
French dressing	2 tablespoons	296
Cabbage	50 gm.	3
Butter	10 gm.	30
Bran biscuit		
Black coffee		
1 egg	50 gm.	83

SUPPER		
Bouillon	180 c.c.	
1 egg	50 gm.	83
Bread	30 gm.	81
Butter	20 gm.	160
Lettuce	30 gm.	
French dressing	2 tablespoons	296
1 orange	250 gm.	96
Total calories		1,534

March 14 his acidosis had disappeared. He continued to do well on this diet until about March 25, during which period he frequently walked with assistance, progressively better, his movements being limited only in range of action and the power with which they could be executed. At about the date mentioned, he developed pain in the left chest with increased disability of the left shoulder. After being watched for two days, it was believed that this disturbance might be pleuritic, with undesirable consequences, and he was placed on an unrestricted diet. There were very slight fever and signs of a small left sided effusion. The leukocytes numbered about 12,000; the polymorphonuclears numbered about 51 per cent., and the proportions of the other blood elements appeared to be normal. The pleuritic condition subsided. March 31 he developed slight effusion and tenderness of the left knee and April 1 there appeared edema of the left thigh, tenderness above Poupart's ligament, evidence of moderate left femoral thrombosis with fever and a cylindrical tender mass in the upper femoral region. This condition slowly subsided and April 8 it was clear that despite these two exacerbations, motion in the hips and knees was well preserved or even increased. April 15 the following note was made by Major Cleary: "Examination shows that edema of the left leg has decreased definitely, and tenderness has almost entirely disappeared. The range of motion of both limbs gradually gained by the patient up to the time of exacerbations is entirely retained. Within this range, motion is more free than it has been before. The patient moves his limbs with a confidence which indicates much less fear of causing pain. The improvement in this case has been coincident with, and in my opinion due to, the strict dietary restrictions imposed."

From this time on, the patient ingested for the most part an average of about 1,800 calories per diem. April 20, 22, 23 and 24 he again walked across the room with assistance, feeling greatly encouraged at his large increase of potential.

In view of the prospective closure of the hospital and the doubt that still remained as to whether his tonsils constituted a focus of infection, it was decided to remove them as a prophylactic measure. This was done April 27 and April 30 there developed edema of the uvula with a temperature of 101 F. These symptoms subsided in a few days. After tonsillectomy the right hip suffered a slight exacerbation, being more sore than at any time since improvement began. The tonsils showed *Streptococcus hemolyticus* in small numbers and were small and necrotic.

It was plain from a dispassionate survey of this case that the régime instituted resulted in abrupt return of motion in previously ankylosed hips and knees, and the patient, from having been utterly bed-ridden, was able to get out of bed and into bed without assistance, to walk freely with crutches, even getting around with a cane and the support of objects in the room. There was no doubt of his betterment and prospective further improvement, and he was reported as doing very well three months later, August, 1919.

As is fully described under the section treating of blood sugar, this patient had a very low sugar tolerance and the fact that the tonsils played a rôle as focal agents is indicated by the return to normal of his sugar tolerance after their removal. It is possible that an error was made in not removing them at the outset, but subsequent events indicated that his return of function was more rapid under dietetic treatment before his tonsils were removed than was increase of function (when he had already made marked improvement) after his tonsils were removed. As also indicated elsewhere, the persistent low sugar tolerance in this case, in the light of later events, afforded some evidence that all foci of infection had not been removed. It is to be noted that his improvement under dietary régime was emphatic, even in the presence of what was apparently focal and even causative infection. This case was highly illustrative of the abrupt and marked improvement which can be brought about in properly selected cases, even in the presence of long standing arthritis, amounting clinically to ankylosis. Whether the attacks simulating, respectively, pleurisy and phlebitis were referable in any way to the period of underfeeding cannot be settled definitely. It does appear, however, that they were rheumatoid in nature, and it is in line with my experience with other cases treated less radically in the same way, that, after a sharp initial improvement, there may ensue, at later stages, exacerbations at one or more sites which continue decreasingly until the patient is well established in convalescence. It is in this connection that unpleasant consequences might follow the application of low diets to patients the subject of anemia, inanition and the like. These exacerbations, however, in properly selected subjects, such as the present one, are no greater than occur in any event; they grow less frequent and severe, and they may be absent altogether. It is probably somewhat because of the contrast with betterment that they attract attention. This patient was treated by more heroic measures than I had exercised before, and it is not recommended that they be adopted without full deliberation, and only then in proper cases.

One of the conclusions developed, therefore, as the result of this experience in the dietetic handling of arthritis not amenable to other forms of therapy, is the fact that in certain cases the period of reduced diet may be advantageously ushered in by a short period of sharp fasting. There are limitations to the degree to which this may be pushed, notwithstanding occasional striking improvement at the outset, because too much undernutrition may retard rather than assist the later response, which must be sustained to be effective. Too much stress cannot be placed on the fact that only selected cases, patients in a state of good general nutrition, should be subjected to this initial procedure. The methods necessary to achieve permanent benefit along dietary lines

should not be adopted unless there be available experience with the confusing sequels of arthritis, which often simulate active disease, and experience with nutritional problems and the calculation of accurate diets. I have endeavored to point out elsewhere with all possible emphasis, that such procedures constitute a two-edged sword capable of evil as well as good, and likely to result as much in evil as in good, unless appropriately applied.

The preceding experiences with diets should not be viewed as isolated observations. They should be interpreted as part of a considerable series of cases treated on the same principle under changing experimental conditions, as previously reported.[13]

In the subsequent light of the slow response of a number of cases to other measures, it is regretted that more patients were not so treated, but as already mentioned, this therapy was reserved for the most refractory types because of the time and cooperation required. It should never be resorted to alone in the presence of removable foci of infection. It affords a means, however, by catering to a weakened function, of reaching many cases that have responded to no other efforts, and it is clear that it can also be used to good effect, although only in properly selected cases, in conjunction with other measures.

In working with numbers much greater than make up this series, it is probable that one or two fixed, graded diets could be used to advantage, but the problem of the arthritic is an individual one, diagnostically and therapeutically, and much the same limitations obtain as would in attempting a similar control of diabetics.

In view of the fact that there was indicated by the nephritic test meals a slight retention of salt by the kidney, two patients were placed for periods of two weeks on salt-free intake, one as a therapeutic test, and the other partly for that purpose and partly to facilitate absorption of an edema of the leg, but no therapeutic effect on the arthritic process was observable in either instance.

LOCAL AND EXTERNAL MEASURES

As already mentioned, the subjects of this study showed a greater tendency towards recovery than do similar cases under civil conditions occurring in the later decades of life. Probably because of this, they also showed a surprising response to local and external measures, comprising chiefly baking, massage, hydrotherapy and electricity.

Many patients recovered entirely in spite of neglect that was probably unavoidable. Many on the way to recovery were hastened in their convalescence by the vigorous institution of local measures, particularly massage and baking. In some cases, benefit and symptomatic cure followed almost at once after a long period of invalidism. Many cases

gave clear evidence of benefit from such measures at hospitals established at the watering places of France and elsewhere, and there was no room for doubt that full utilization of these adjuvants was often productive of good. It was a matter of difficulty, however, to attach the proper importance to any or all of these agents. The single statement in regard to their utility that can probably be safely made is that they should be regarded as adjuvants rather than as the fundamental bases of therapy. These measures all have at least one element in common, the induction of hyperemia, and their field of application as previously mentioned is properly in cases which tend to recovery, cases of mild degree and cases in which the basis of convalescence is already laid. They can also be used with propriety in adding to the comfort of more severe refractory types in which, however, their curative effect is slight or absent.

If it were necessary to select one of these measures as that which alone could be applied, the first choice would probably be baking; on the one hand, because of the benefits to be derived, and, on the other, because of the relative ease of application by means of small portable units or home-made measures. This is particularly true in view of the etiologic rôle played by exposure in this series, and many subjects dated improvement from their return to conditions of warmth and dryness.

The application of massage to the subjective and objective disabilities consequent on "rheumatism" and arthritis is too widespread to call for much comment. Many of the sequels of arthritis are similar to those following trauma and other factors within the orthopedic field, and in this connection massage accomplishes some of its best results. The disability originating from contractured tendons, thickened capsules, etc., may so closely resemble, in respect of pain, that due to active arthritis per se, that the greatest skill is sometimes required to differentiaate them. This field, however, is so familiar to qualified orthopedists, that it is unnecessary to enter on it at length except to emphasize the importance of interpreting properly the indications for and against massage. Probably one of the most common errors in treating arthritis is in the application of massage to a chronically but actively inflamed joint, thereby adding mechanical trauma. Deep massage to the large muscles was useful where they needed development and where locomotion was being encouraged.

It is, perhaps, pertinent to mention at this point that a desirable result achieved by any or all of the external measures above enumerated in the care of soldiers, was that of giving them the sense of being actively treated. In a disease of such chronicity, in which much time is sometimes required to demonstrate even the failure of a given line of

therapy, the importance of giving these men this satisfaction and of affording them at least momentary "bien aise" is not to be discounted. It is something of a commentary on the lack of systematized treatment of arthritis in general that many of these men had been through ten or fifteen hospitals and complained of having had no treatment of any kind, except rest in bed. Their satisfaction with these objective procedures when practiced at U. S. Army General Hospital No. 9, brought this point to our notice, although a comparable satisfaction on the part of the public at large is common knowledge.

It was also difficult to place a proper value on hydrotherapy and the sweating or eliminative processes so frequently employed in the treatment of arthritis.

The available evidence suggests, as mentioned in the chapter on renal function, that the chief factors active in producing benefits under these conditions are those to which the sweats are incidental. In other words, raising the body or local temperature to a point higher than normal, results, in the former case, in increased metabolism; in the latter case it results in hyperemia and possibly locally increased metabolism as well. It is important, therefore, not to confuse cause and effect. It is entirely possible that other factors are operative, such as the changes in the fluids of the cell induced by diaphoresis, but this is independent of the question of elimination, per se. The possibility of benefiting certain patients by these measures, however, cannot be denied. The facilities available permitted only of the use of whirlpool baths for single limbs, together with the various general douches, and these were developed only shortly before the closure of the hospital. The local whirlpool baths were productive of good results and were generally enjoyed by the patients. They were much to be preferred to hot packs in bed and were also more easily productive of about as much free perspiration as followed the latter measures. Before the instalment of whirlpool baths, however, hot packs were resorted to with some success.

It is probably even more difficult to estimate the alleged value of the various electrical treatments than is the case with any of the other measures mentioned. In so far as electrical therapy depends on the induction of muscular contraction, and in so far as it was depended on to raise the temperature of a part locally either by placing it in a bath or by passing the current directly through the part, the indications for its use were clear, and it supplemented other measures advantageously. Opportunity did not permit, however, of giving the attention necessary to weigh the benefits alleged to accompany other forms of electrotherapeutics. It is hardly to be doubted that the metabolism is importantly altered systemically as well as locally through various activities

of this kind, but this field needs study at the hands of critical clinicians together with coincident careful laboratory work in several directions.

Of the measures above described as being useful in the treatment of chronic arthritis, electricity in its various forms supplies the greatest psychic influence to the individual. In this respect it plays a useful rôle in the therapy of a disease where chronicity, with resulting lowered morale, is so frequent. Provision for the care of a large group of soldiers the subject of chronic arthritis would probably be incomplete without inclusion of the usual standard electrotherapeutic appliances.

The indications for local and graded exercises were such as are common in orthopedic experience and were met in the usual way as far as the hospital facilities permitted. Outdoor exercise, such as walks and golf, played a limited rôle in the treatment of these men and was resorted to as soon as conditions warranted. It was highly useful in overcoming hospitalism, inducing free perspiration, developing weakened musculature generally, and in putting individuals in condition finally to assume the duties of an active life.

SUMMARY

The purposes for which the present effort was undertaken were three in number: (1) To treat as many soldiers who had arthritis as might be reached through one center established for this purpose; (2) to conduct intensive studies as to the nature of the disease and the best manner of treating it; (3) to consider critically those elements of the problem which have military application with the view of lowering the incidence of the disease, if possible, on the one hand, and, on the other, expediting the return of arthritics to duty, thereby contributing to the number of available men and to a reduction of hospital days and congestion.

The results of this effort can conveniently be grouped under two heads, (1) those of a more or less academic nature bearing on the pathology of arthritis, together with purely medical considerations along this line, and (2) those which concern chiefly the military aspect of the problem in relation to conditions of warfare. The results of the several lines of laboratory investigations undertaken have been sufficiently emphasized in respective chapters dealing with these topics to make repetition of these findings unnecessary. The outstanding facts concerning them will be summarized in the final conclusions.

The purely practical aspects of the question, in relation to the emergency created by the war, however, will bear further emphasis.

Statistical analysis has revealed, as indicated under that caption, that 36 per cent. of the 400 patients presenting on the arthritic service

at U. S. Army General Hospital No. 9, had had previous attacks of rheumatism. In contrast to this, only 7 per cent. of 113 cases analyzed on the orthopedic service had had previous attacks of rheumatism, and these latter figures are borne out by statistics compiled by Capt. Bertnard Smith, M. C., chief of the Cardiovascular Department of U. S. Army General Hospital No. 9, which indicates that in less than 6 per cent. of 350 cases of functional cardiac disorder, was there obtained a history of "rheumatism" before admission. It is clear that something induced previous attacks of arthritis or rheumatic disability among the subjects of this study with a frequency five times greater than obtained among soldiers at large.[19] The thought is at once suggested that the incidence of arthritis in the army would be reduced by rejecting, at the time of an incoming draft, all men giving a definite history of arthritis or "rheumatism." That this would accomplish the purpose in mind is hardly to be doubted, but it would probably, at the same time, needlessly cut down the number of recruits.

In view of the fact that one outstanding tangible factor in the production of arthritis at large is focal infection, it would seem a justifiable recommendation, were the war still in progress, that recruits giving a definite history of previous attacks of a rheumatoid nature, should be segregated for careful analysis as to obvious foci of infection.

It would seem reasonable to be guided by the severity and frequency of the previous attack, rejecting absolutely extreme instances, and segregating for examination those of a milder nature. Although all recruits admitted to the army are supposedly examined as to their teeth, ears, throat, etc., this examination, in the nature of things, is not adequate to cover the point at issue. There is little doubt that routine analysis of a group segregated for the above purpose would reveal at the hands of qualified examiners, bearing this point in mind, an appreciable number of potential and causative surgical infections. Our statistics show that 73.25 per cent. of all men admitted to the arthritic service were the subject of demonstrable surgical foci of infection. The possibility, therefore, that foci played a rôle in the etiology of arthritis among the 36 per cent. of men having had attacks prior to their army service, is obvious.

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19. Organic heart disease is to be excepted. A personal communication through the courtesy of Captain Smith just quoted, indicates that of 150 patients with organic heart disease 42.9 per cent. (64 cases) had had acute rheumatic fever either before or during military service. Of these 64 cases, 23.4 per cent. (15 cases) had had no attack before entering the army. In other words, of 150 cases, 32.7 per cent. (49 patients) had attacks prior to army service, a proportion slightly lower than in the case of arthritis (33.75 per cent.). In point of fact, these two sets of statistics in some part cover the same field as many forms of organic heart disease are notoriously of "rheumatic" nature and origin.

Following the determination of focal infection in draftees who had had previous attacks of rheumatism, it would be possible, then, to anticipate the steps which became necessary eventually in the case of all soldiers in this series who had not recovered on admission to the hospital; namely, the removal of demonstrable surgical foci.

A precedent in the recommendation of dental attention, when necessary, has already been pretty widely established on grounds of general prophylaxis alone, and the experience of the warring countries has shown that efforts at conservation of this nature would have added justification as continuation of the war made further demand on the available man power. The action here suggested constitutes a more critical application of an existing precedent to achieve a specific rather than a generic purpose. The degree of success which would follow institution of such measures could be determined only by experience, but that an important reduction in the incidence of chronic arthritis would be achieved by the specific application of these means is hardly to be doubted.

As the statistics show, 71 per cent. of all foci were tonsillar (52 per cent. of all cases); 45.7 per cent. of all foci were dental (33.5 per cent. of all cases). The tonsillar foci would necessitate an operation for their removal with consequent hospital days, and could await a time of election. The removal, however, of dental foci, which the statistics show were practically invariably abscesses at the roots of the teeth, could be accomplished in most cases without difficulty or delay. Genitourinary diseases have apparently played such a small rôle in the etiology of the present series, that the importance of instituting analogous action in regard to them is not so great, although the same procedures could be followed.

The rejection of extreme instances and the examination and subsequent treatment of draftees giving a history of "rheumatism" and bearing surgical foci, would leave a group in which no infection could be demonstrated. It would seem justifiable, in connection with this group, to be guided solely by the severity and frequency of the previous attacks, rejecting from service those cases in which these factors were marked and accepting for service those men who were in apparent good health and had had no recent disability of this nature.

As mentioned in the opening chapter, the number of cases of chronic arthritis to be expected in an army of 4,000,000 men is so considerable, and is so substantiated in respect of numbers and severity by the studies herewith presented, that it must be concluded that chronic arthritis constitutes one of the outstanding medical conditions affecting the soldier in service, particularly under conditions of active

warfare in the field.[20] It is probably fair to say, that the magnitude and importance of this problem have been somewhat overlooked in the emphasis placed on other, sometimes less considerable, conditions. The problem from the purely numerical standpoint is not equal in size to that presented by the acute infectious diseases at large, particularly in the camps of this country, but it is to be remembered that, for the most part, the subjects of the acute infections recovered or died; a relatively small percentage returned to civil life incapacitated. The subjects of arthritis, however, not only run a course exceeded in length by few conditions affecting large bodies of men, but carry into civil life, in regrettable proportions, conditions which incapacitate them for a long time or even result in permanent disability. That they do better as a class than do cases of equal severity in the later decades of civil life does not remove the problem. The impression was forcibly borne in on us in the course of these studies, that subjects of an arthritis of even moderate severity were often more incapacitated and for a longer time than were soldiers who had suffered an amputation. The patient who has had an amputation is at least in good health and can devote his energy to the tasks allotted him. The victim of an arthritis is not only incapacitated to a comparable degree, but is additionally suffering pain and discomfort. Carefully considered efforts at the prevention of this disease would have large justification.

As mentioned earlier, the purposes of this study included making overseas, at the site where most cases developed, adequate provision for meeting this problem along lines most clearly indicated. Any such plan would have called for centers for the segregation and treatment of these patients and a base or bases where the more refractory types could receive detailed and thorough care. In addition, there has been indicated the necessity in this country for analogous distribution and care of these subjects, including those returned from overseas.

Fundamental to successful treatment of this large group of men is adequate provision of medical personnel and physical facilities in the way of at least the simpler forms of baking, hydrotherapy, etc. It is not to be expected that at subsidiary centers much could be developed

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20. Through the courtesy of Col. A. G. Love of the Sick and Wounded Division, Office of the Surgeon-General, Washington, D. C., data have been obtained, based on the year 1918, which show an incidence of about 35,000 cases for an army of 4,000,000 men for one year.

It is to be borne in mind that in only about five months of this year were United States forces engaged in active warfare on a large scale. Furthermore these figures are for primary arthritis only and not for rheumatic fever or arthritis complicating any other disease, although it is clear from the present studies that many, if not all, cases of rheumatic fever also belong in this category. In view of these considerations it seems fair to postulate an incidence of 40,000 or more cases of all types for an army of 4,000,000 men for one year.

along these lines but it should be possible in any base hospital to which these men are first admitted, to discover and remove obvious focal infection. The failure to do so was an omission frequently illustrated in the present series. The prompt recovery of certain soldiers, who had been invalided for variable periods of several months or more, on the removal of easily demonstrable foci, proved beyond doubt that many patients presenting foci on admission had been neglected. It was clear that considerable attention had been paid to foci as etiologic factors, but appreciation of their rôle does not necessarily afford the experience requisite to discover and remove them, nor can the best intentioned and most skilful medical officers care for more than a limited number of patients. It was obviously due, in part, to this fact, that under the stress of warfare many patients suffered unduly. The evidence obtained from the histories of many of these men, however, makes it plain that no systematic and regular policy was followed in regard to them and that such cases were probably not unfrequently regarded as of secondary importance or too refractory to warrant much emphasis.

It is quite clear, therefore, that were the war still in progress something real could be achieved by emphasizing and systematizing the treatment to be given these men on their admission to the first hospitals that could properly undertake such work.

The problem of the personnel and equipment to be provided at the bases is an important one. The results of this study suggest that it would have had to be met on a large scale. Sufficient space has been given to the various forms of treatment to indicate that the external forms of therapy, which in civil life so frequently meet with disappointing results, must be accorded greater value when considering this group. It is believed that this point should be emphasized as a practical measure of large importance to the conditions under discussion. It is possible that such saving of effort could be achieved, as was apparently attempted, by establishing such bases at existing water resorts, but this consideration alone should not be allowed to dominate. In a disease in which improvement or cure sometimes depends on the coordination of a number of factors, each of limited value alone, advantage should be taken of every condition known to have favorable influence. Among such conditions is the question of climate. Students of arthritis would probably agree that a damp enervating climate is undesirable and that low valleys and the sea coast should be avoided as sites for treatment. The present observations at U. S. Army General Hospital No. 9, were carried on in the midst of a thick pine belt on a sandy soil which quickly absorbed moisture, but there was no altitude and the sea was only nine miles away. Our experience has

shown that although the dampness and the abrupt changes of temperature were much modified, climatic conditions were not ideal. It is quite clearly indicated that the most desirable site for the establishment of a treatment center for arthritis is inland, in a dry region of fairly equable climate, with reasonable altitude of, say, 600 feet; a greater altitude would be advantageous.

Coordination of the many agents which have application to arthritis, rather than dependence on one or two measures, constitutes a desideratum emphasized by this study. In few centers for treatment is this attempted to an important degree because most of them are dependent upon and due to the partial success of measures developed locally.

Success in coordination depends on competent direction, in the first place, and on the caliber of those conducting the various accessary activities drawn on, in the second place. Perhaps no other disease demands more in this connection. Experience in civil life and with more than 400 cases in this series has shown that this latter conclusion is particularly true of the specialties of the nose and throat, and of dentistry. The recognition of causative foci in the throat and head requires the widest possible experience.

Treatment of the sequels of arthritis has so often necessitated painstaking and patient efforts on the part of orthopedists, that the burden of care for all parts of this important field in civil life has fallen on them more frequently than on internists, with the result that some of the most important contributions to pathology and treatment have originated with orthopedists. The problem of arthritis, however, is fundamentally medical, and it should be necessary to call on orthopedists only to differentiate doubtful conditions, and to care for the sequels of long standing processes. The importance of orthopedic cooperation must not be overlooked, however, in considering this subject from the purely medical viewpoint. The many cases analyzed during the present study have served to indicate that it would be impossible to give adequate care to arthritic soldiers under warfare conditions without assistance from experienced orthopedists. For example, the attempt has been made under the caption "clinical considerations" to emphasize the difficulties of differential diagnosis in certain types of cases, particularly those with disabilities referred to the back. The field included here is very large and it is easy for the internist to overlook pathology of an orthopedic nature and to make incorrect diagnoses. The roentgen ray is of very limited assistance in these relatively early cases, and the factors actually producing sciatic pain, sacroiliac, paravertebral and even vertebral pain are often difficult of analysis. In addition to the necessary cooperation just indicated, it is obvious that adequate orthopedic assistance is essential for cases needing immobilization, extension, braces and the like.

Provision for the routine examination and ward care of arthritics is not as simple as may appear. These steps must precede all others and determine the lines of treatment finally followed. It is difficult or impossible for the chief of a large arthritic service to keep before him the detailed needs of such cases, although many of them call for long experience in their proper classification and disposition. Such action must fall in general on younger and less experienced men. No systematized plan of treatment of arthritis has been evolved to date, and results from any and all measures have so frequently been disappointing as to produce confusion and a general attitude of indifference or even hopelessness among all concerned. On the other hand, the topic of arthritis enters a variety of different and opposite domains of medicine and surgery, some of which are apt to believe that they hold the key to its solution. Clinical manifestations of the disease generally concern structures primarily within the field of orthopedics, and interest on the part of medical men in the underlying pathology is often wanting. As just mentioned, however, the disease is properly comprehended by internal medicine and the final solution of its etiology, prevention and treatment must be sought for in clinical and laboratory investigation, proceeding from this premise. Notwithstanding the omnipresence of this disease it seems that physicians are too rarely accustomed to interpret critically the symptoms of these patients; to classify the types encountered, and to employ the desired discretion in the forms of treatment adopted. Apart from the shortage of well trained medical men in the army hospitals at large, it is probable that a difficulty in making adequate provision for the treatment of arthritis on the large scale which continuation of the war would have necessitated, would lie in obtaining medical officers whose previous interest in this field would find added stimulus in the large opportunity presenting. Without an interest below the surface, the routine care of arthritics soon becomes monotonous to the detriment of the patient. The problem of the arthritic is largely individual; in this it is somewhat comparable to the problem presented by the various forms of neurasthenia which the war has produced in such large numbers, and cannot as yet be met by wholesale measures alone.

CONCLUSIONS

1. Chronic arthritis is one of the larger medical problems affecting the soldier in service. Soldiers developing it have had previous attacks with a frequency about five times greater than have soldiers admitted to hospital for other conditions at large.

2. Exposure was the exciting factor in 58 per cent. of 400 cases studied. Critical examination of all patients revealed apparent foci of infection in 72 per cent. Although the etiologic importance of focal

infection, especially in civil life, is not to be minimized, it is clear that the present group showed a considerable independence of it. One hundred and eighty-four patients, or 46 per cent., recovered in the presence of demonstrable surgical foci. This is nearly three times the number which improved (sixty-five cases, or 16.25 per cent.) after the removal of foci. The tonsils were most frequently the site of infection (52 per cent.); the teeth were next (33.5 per cent.); the genito-urinary tract came last (12.5 per cent.) and clearly played an almost negligible rôle in causing arthritis.

3. The sites of most frequent involvement were the knees (62 per cent.), the ankle (35.25 per cent.), the hip (33.75 per cent.) and the shoulder (31.25 per cent.). All things considered, however, it is not clear that trauma to weight bearing parts, caused by hiking, drilling, etc., played a much greater rôle than it does in civil life in determining the site involved.

4. The basal metabolism was found to be normal in 80 per cent. of twenty-nine cases studied. In 20 per cent. it was slightly below normal limits.

5. The carbon dioxid combining power of the blood; the total fat; the cholesterol and the calcium of the fasting blood were found to fall within the accepted normal limits.

6. About one half of forty cases of arthritis studied showed an abnormally high value for blood creatin. Certain of these showed a decline in blood creatin coincident with clinical improvement.

7. The urea of the fasting blood in seventeen cases fell within normal limits. The nitrogen of the fasting blood in sixty-seven observations in fifty-seven cases fell within normal limits, with two exceptions.

8. Studies of the renal function, in thirty cases of arthritis of widely different types, by means of the so-called nephritic test meal, gave results which fell within the accepted ranges for normals. When compared with nine normals under similar conditions there is evident a slight lag in the elimination of water, nitrogen and particularly of salt. In conjunction with the normal blood nitrogen and urea values mentioned in the last paragraph, it seems fair to conclude that there is no marked dislocation of renal function in chronic arthritis, though this function may be slightly lowered in some cases.

9. In studies on arthritics representing all degrees and stages of the disease it was found that there is a lowered sugar tolerance in a large proportion of cases. This lowered tolerance accompanies the great majority of severe cases and is roughly proportional to the activity of the arthritic process per se. It returns or tends to return to normal with convalescence or recovery.

10. The return to normal is apparently independent of the type of therapy employed, but is most abrupt after the removal of causative

foci of infection. In certain severe chronic cases from which all demonstrable foci have been removed, a lowered sugar tolerance seems to persist.

11. Apparent foci of infection, unproductive of systemic effects, are not necessarily accompanied by a lowered sugar tolerance. A lowered sugar tolerance from focal infection apparently accompanies the failure of the organism successfully to maintain its wall of defense. In this light a lowered tolerance becomes an intermediary step in the pathology of arthritis and possibly other conditions as well.

12. A lowered sugar tolerance seems to stand in relation to many infectious or inflammatory conditions at large, and to depend on more fundamental pathologic processes than has been appreciated. It is also of more common occurrence than has been recognized.

13. The lowered tolerance observed in some diseases and referred to them may sometimes have been due to focal infection rather than to the diseases under consideration. It is important that foci of infection be eliminated from consideration when miscellaneous conditions are studied in this regard.

14. Critical examinations of recruits for a history of previous attacks of arthritis would reveal cases most likely to develop it. It is reasonable to believe that rejection of this group or at least the worst cases in it would importantly reduce the incidence of arthritis in the army. A more conservative policy would segregate such cases, examine them for foci of infection and remove such foci when found. This would have the added importance of prophylaxis towards the civil community. These measures could be combined by applying one or the other appropriately.

15. The several forms of therapy here discussed have all application to the group under consideration. Treatment of large numbers of cases, however, requires methods capable of wide routine use. Local and external measures in the sense indicated have unexpectedly large application because of the tendency of this group to improve under favorable conditions; they are also susceptible of easy routine employment.

It seems that in some cases of arthritis in this series six months or a year were needlessly lost. Earlier and more critical attention to focal infection, as a basis, together with a large coincident use of local measures, would probably afford the routine therapy best adapted to reach the greatest number of cases and should importantly curtail the existing invalidism. Many patients would require more individual attention, however, such as treatment by nonspecific protein injection or a restricted diet.

16. Experience with treatment by a restricted diet, as here described, corroborates in the present group, the conclusions previously published regarding it. Such therapy finds additional support in the studies on blood sugar, revealing a difficulty in the utilization of carbohydrate. It seems clear that success following this measure depends on catering to a weakened function of which the lowered sugar tolerance is one evidence. Treatment along this line has undoubted application in appropriate cases of chronic arthritis.

17. The several measures of value in arthritis should be combined in their application to the present group more frequently than obtains in the treatment of cases in civil life. The tendency to focus on one measure often results in failure where the subsequent coincident use of several measures results in benefit.

The foregoing report would be incomplete without acknowledgement in many directions; especially to Col. Warfield T. Longcope, M. C., U. S. Army, and to Col. Lewis A. Conner, M. C., U. S. Army, successively heads of the division of internal medicine, Office of the Surgeon-General, Washington, D. C. To Colonel Conner is due much obligation for support throughout the period of work.

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Appreciation should be expressed to Col. Charles Field Mason, M. C., commanding officer, U. S. Army General Hospital No. 9, Lakewood, N. J., for his uniformly helpful attitude, and especially to Lieut.-Col. J. C. Gittings, chief of the medical service, for cordial and able assistance in both administrative and medical matters.

Finally, it is a pleasure to mention again the cooperative support of Major E. W. Cleary, chief of the surgical and orthopedic services, and to acknowledge the assistance of the medical and nursing staff of the hospital, without whose willing help much of this work could not have been attempted.

CLINICAL ABSTRACT OF CASES

The large numbers refer to the hospital register number. This list includes nearly all cases which were the subject of laboratory investigation. A few other cases are mentioned in the text, but not included here, as the data accompanying them are sufficiently full for the purposes intended. The hospital register number is missing in a few cases owing to the inaccessibility of records following closure of the hospital.

CASE 1 (No. 2656).—Lieut. Robbins, aged 25. One previous attack of rheumatism nine years before, lasting three months. After two months of pain in right shoulder attributed to bayonet drill, he was taken sick in September, 1918, with swelling and pain in the left ankle for which he went to the hospital. Involvement of other joints was progressive, finally affecting the right shoulder, right foot, knees, hips and scattered muscle groups. On admission to U. S. Army General Hospital No. 9 he had had one tooth extracted for an

apical abscess about eight weeks previously, without benefit. There was apparently no other focus of infection, the tonsils being repeatedly pronounced normal. This officer made a complete recovery by dietary measures alone, improvement dating abruptly from their institution. Details are given under "Dietary Considerations."

CASE 2.—Karl Haeberle, aged 26, white. No previous attack. While drilling on rough ground May 2, 1918, the right ankle became swollen and painful. This case ran a long chronic course suggestive of tuberculosis. He failed to improve following tonsillectomy, one month after onset, with attention to abscessed teeth. There was much edema; elevation and rest proved of no avail. The final diagnosis of an unusual type of bone atrophy following trauma was made by Colonel Brackett, division of orthopedic surgery, Surgeon-General's Office, and under his advice the patient was given exercise. The foot then improved and on closure of the hospital in June, 1919, he was well on his way to recovery. He was again seen in November, 1919, and had made further marked improvement, the foot appearing nearly normal.

CASE 3 (No. 2485).—Blowers, aged 24, white, infantry. December, 1917, he sprained the left ankle. While in the hospital for treatment, he developed rheumatism in the legs extending to the right knee, hand, elbows and fingers. He made a fair recovery within several months; but about six weeks later he was again taken sick. There were no demonstrable foci of infection and on discharge, about January, 1919, the patient had made recovery to the point where his disabilities were muscular, with occasional stiffness and pain on climbing stairs, which condition remained about stationary.

CASE 4.—John McGrann, aged 44, white. Following gunshot wound of back was taken sick in July, 1918, during convalescence, with pain and weakness in the muscles of the back and spine. The roentgen ray showed arthritis of the spine. No foci of infection were detected, except, possibly, in the gums, which were in rather poor condition, and in pockets about the teeth. These received attention and he made a slow and limited improvement of about 60 per cent., being discharged about April, 1919.

CASE 5 (No. 2583).—Beck, aged 26, white. Previous attack of multiple arthritis three years before, which followed three months after a gonococcal infection. He was accepted for full duty, and at the end of September, 1917, following a cold, he was affected by swelling and pain in the knees and ankles, but improved enough to embark for France, but was again taken sick on ship board with extension of the rheumatism to the right shoulder and the hands, since when he did no duty. This patient made a limited improvement following tonsillectomy, August, 1918. Attention to his teeth in November, 1918, was of further value, and he was apparently well when discharged, Jan. 2, 1919.

CASE 6.—William Hayes, sergeant, aged 29, white. In 1916, he suddenly developed arthritis of the left foot and wrists extending to the fingers and knees. Under treatment at Hot Springs the foot recovered, but after some improvement in other joints he again grew worse, the right wrist becoming ankylosed. Tonsillectmy in December, 1918, and attention to the teeth were without benefit. This patient made an abrupt 50 per cent. improvement under dietary measures to which were later added potassium iodid, cod liver oil and daily sweats. He left the hospital symptomatically well in May, 1919. This case is described in full under dietary considerations and was very instructive throughout, illustrating what can be achieved in the most severe types by combinations of treatment, if the basis for convalescence be established.

CASE 7.—Ben Jaffy, aged 24, white. Previous attack of arthritis of right knee in 1913, confining him to bed for four months. The present illness began in the right shoulder in July, 1918, following exposure. A tonsillectomy had been performed in 1913. On admission the knees and shoulders were markedly involved, and he presented focal infection in one abscessed tooth, which was extracted December 20. He made a rather abrupt improvement following

this, and then remained in statu quo for a number of months. Improvement did take place, however, and in May, 1919, he was discharged having made about 75 per cent. recovery and was still improving.

CASE 8.—Albert Martin, aged 44, white, was taken sick in March, 1918, with arthritis of the right ankle and knee extending to the hip. He became bedridden, and his case ran a protracted course without the slightest improvement. There were foci in the tonsils, which were removed Dec. 30, 1918, without benefit. There was evidence of renal calculus, and the liver was enlarged four finger breadths. The physical and mental condition of the patient were not suited to radical therapy or that requiring his cooperation. This case was one of the most advanced and refractory in the entire series.

CASE 9.—Enrique Beeman, aged 24, white, gave a history of previous disability in the hips and sciatic region. The present illness began acutely in February, 1918, following drilling and exposure, and affected the left hip, right ankle and the back muscles. He made an essential recovery, but because of residual symptoms, tonsillectomy was performed Dec. 2, 1918. Six weeks later, this had apparently had no influence, and he was discharged complaining of shifting and intermittent disability in muscles of back and legs.

CASE 10.—Naseeb Masood, aged 23, white, had had no previous attacks. In April, 1918, he was gassed and underwent exposure in the trenches, following which there developed arthritis in the hips, knees, ankles and back. Since this date he walked only with crutches, remaining a bed-ridden patient until discharged from the hospital. There was definitely no dental focus; genito-urinary examination was negative and his tonsils were removed Nov. 15, 1918. This was without the least effect, and his condition was the same on discharge, March 2, 1919. This case was of much interest in that the patient's disability consisted in exquisite tenderness on active or passive motion of the knees or on palpation. There was also exquisite tenderness at the metatarso-phalangeal articulations of the feet. The roentgen-ray findings were negative and a marked psychic element was suspected, but he gave repeatedly a greatly lowered sugar tolerance, and it seems proper to regard this case as one of marked severity of the fibrous type, giving little or no contracture or roentgen-ray changes and running a protracted and obstinate course.

CASE 11.—George Hinman, aged 25, white, was taken sick gradually following exposure, February, 1918. After improving, he was again taken sick with arthritis involving the knees in August, 1918. His chief symptom during observation consisted of slight disability of the right knee and intermittent sharp exacerbations of arthritis in one or the other wrist, accompanied by redness and swelling; the roentgen-ray findings were positive; all foci were reported negative. This patient made a modified improvement under a slightly lowered fixed intake of food, but the results were not sufficient to warrant a detailed report, as he developed acute tonsillitis following which tonsillectomy was performed April 2, 1919. The tonsils were found to be diseased and the patient thought he felt a definite improvement following their enucleation.

CASE 12 (No. 2662).—Thomas Boyd, aged 24; white; began to have attacks of rheumatism nine years before, being in bed frequently for from four to six weeks. He had had no attacks for the last three years, but had had three or four attacks of tonsillitis. He did full front-line duty in the trenches. While drilling in rest camp in April, 1918, he began to have pain in the muscles of the legs and later in the back, often accompanied by febrile exacerbations. Tonsillectomy was performed Nov. 4, 1918. He had no dental or genito-urinary foci but was definitely not cured by this procedure when discharged March 10, 1919.

CASE 13.—Mrs. Lum, aged 42, white. This woman had had arthritis for nine years, with deforming arthritis of the hands and wrists and was studied by permission of the commanding officer. She had had exhaustive attention given to all foci without avail, and her tonsils were repeatedly pronounced so small

as to be almost absent. Among operative procedures to remove foci were appendectomy and cholecystotomy, but the gallbladder was normal. Tonsillectomy was performed in June, 1919, as a routine procedure. Culture was negative for hemolytic streptococci and she was no better in February, 1920.

Case 14 (No. 3559).—Lowe, sergeant, aged 42, white. In 1916 he had rheumatism in the ankles, knees and wrists, bilateral, with a severe attack in June, 1917, but he recovered from this. October, 1917, the present attack began. His tonsils were removed about July, 1918, without any improvement, and he had no other foci. This case was one of great interest and was apparently an extreme example of the fibrous type, accompanied by few or no external evidences and only slight changes shown by the roentgen ray along the shafts of the phalanges of the hand. An osteophyte was removed from one heel in 1917. He was subjected to no less than thirteen different kinds of treatment, including baking, sweats, nonspecific injections, etc. He thinks the protein injections made him worse There was not a little analogy between this case and Case 10 (Masood) which was not, however, so far advanced. Because of a small nasal polyp, operation was directed toward its removal and treatment of the ethmoid air cells, but without obvious results. This patient was exquisitely tender wherever touched on his hands, knees and feet and although able to move slowly, he was essentially chair-ridden. His mental outlook was excellent, and there was no psychic element. The failure of benefit under a short period of restricted diet is described under dietary considerations. He gave a number of different interesting laboratory findings.

Case 15.—Arthur Studebaker, aged 23, white. This soldier was big and well built. He contracted measles at Camp Sherman, May 23, 1918. After nearly three weeks in the hospital, he was discharged, but got wet sleeping in a tent and was taken sick with swelling of the right knee and the ankles, and the left hip, with fever and pain. After much improvement under salicylates, a tonsillectomy was performed about July 1, 1918. An apical tooth infection was removed, but without hastening the rather slow recovery. The right knee remained painful, and the knee was put in a cast for three weeks, after which another cast was applied for three weeks again. He thinks this made him worse, as also did hot fomentation, rubbing and baking. On admission to U. S. Army Ceneral Hospital No. 9, Jan. 9, 1919, his knee was exquisitely tender to touch, with limited function but no deformity or visible objective evidences. Tenderness apparently followed the synovial membrane extending up over the area of the joint capsule. It is possible that this soldier still presented a small dental focus on his discharge, in the condition described, about Feb. 1, 1919. His case was apparently identical in nature with Cases 10 (Masood) and 14 (Lowe).

Case 16.—Br., aged 45, white, civilian. He had had for nearly fifteen years a progressive arthritis, characterized chiefly by intermittent incapacitating exacerbations with sciatic pain and malaise in the interim. This case had been exhaustively searched and treated for twenty-four months on the basis of focal infection. The tonsils were removed, the genito-urinary tract was given much attention and all dental factors were cared for. All these activities availed only to induce a slight improvement, and the severe exacerbations continued. Under a restricted diet this patient made an abrupt and gratifying convalescence, amounting to a 90 per cent. cure, and again resumed his full legal practice with greater energy than he had felt for fifteen years. Observation of this case for about three years reveals that this improvement is maintained and unmistakable. The facts of this case admit of no ambiguity. The greatly lowered sugar tolerance obtained, illustrates, apparently, together with other cases, that the lowered tolerance may persist in the absence of or after the removal of all demonstrable surgical infection. He was studied by permission of the commanding officer.

CASE 17 (No. 2976).—Faulkner, aged 20, white. In January, 1918, several weeks after an injury to the left ankle, he developed pain and swelling in the ankle, knees and right hand and finally nearly all joints were involved. Tonsillectomy was performed Jan. 9, 1919, although at that time he had made a very substantial improvement which seemed to relate chiefly to the change of climate in coming from Camp Shelby. The tonsils were found diseased.

CASE 18.—Samuel Muse, aged 23, colored. This soldier presented widespread tuberculosis of the periosteum and bones of the arm and phalanges of the hands, together with involvement of some of the soft tissues of the arms. The diagnosis was long in doubt; there were exposed and denuded areas of bone, and there was presumably secondary infection. This case was studied as an example of miscellaneous disease. The case is reported here because of the laboratory observations.

CASE 19 (No. 3609).—Fouts, aged 27, white. He had had severe rheumatism of the right leg, thigh and back when 5 years of age. June 9, 1918, there developed, during drilling, disability in the back, right thigh and leg without joint swelling but with stiffness. This man presented on admission, the symptoms of acute myositis of the muscles of the right leg with exquisite tenderness to pressure. Two teeth were abscessed, but there were no other foci, and roentgen-ray examination of the extremities was negative. After critical study this soldier was found to have forward dislocation of the fifth lumbar vertebra, apparently originating from trauma.

CASE 20 (No. 3658).—Wasson, aged 21, white, had had no previous attack of rheumatism and did full duty until August, 1917, when he fell, hurting his right hip. After two or three days he again did full duty. Six weeks later the right hip became painful and a cast was applied. After removal, both knees became swollen and the elbows and fingers of the right hand and wrist became stiff; the right ankle was sore but not swollen. The full differential blood counts were normal, but there were changes in the shape and size of the red blood corpuscles. The platelets were decreased. This soldier was apparently entirely free from demonstrable surgical infection. On admission to U. S. Army General Hospital No. 9 the symptoms in the hands and wrist were intermittent and slight, but the hip necessitated a cast and orthopedic treatment in bed. He was still in bed in May, 1919.

CASE 21 (No. 3645).—Whittington, private, aged 29, white, had had no previous attacks. He did full infantry duty until December, 1917, when he stood in water up to his knees while fighting a fire in France. From this date he had disability progressively in his ankles, knees, hips, shoulders, elbows, wrists and fingers of both hands, with fever. After six or seven months in bed, he improved considerably and on admission to the hospital the chief evidences were in the left knee which was kept flexed. There were diffuse symptoms of varying intensity in the hands and elsewhere, but vertebral arthritis was apparently the most active cause of trouble. This patient had dental, tonsillar and genito-urinary foci when he was taken sick, and their removal was apparently of benefit, although he was still considerably disabled about May, 1919. The greatest relief was obtained from an orthopedic brace.

CASE 22 (No. 3712).—Oberg, aged 24, white, had six previous attacks, beginning in early childhood. He did full duty in the medical corps and after some stiffness in the hips in the spring and early summer of 1918, he was taken sick Aug. 23, 1918, in France, with exacerbation of previous disability and fever. He was confined to bed, and the trouble spread to the left shoulder, and later, after the application of a cast from the waist to the hips, it spread to knees. This case was very severe from the start, and was treated overseas by foreign protein injections which caused severe reaction and increased local tenderness. He also received baking, massage, electricity and other treatments. Examinations at other hospitals had revealed no foci. On admission this patient presented kyphotic ankylosis of the entire spine, great disability

with marked roentgen-ray changes in the left shoulder; complete ankylosis of the hips and practically also of the knees. Shortly after admission an abscessed root was removed with apparent benefit. This patient was treated with interesting and beneficial results by reduced diet. The case is fully described under "Dietary Considerations." He was the subject of many laboratory studies. On his discharge about May 25, 1919, he was greatly improved, could walk on crutches, and had full rotation and increased flexion of the hips and considerable flexion of the knees. The spine apparently presented a bony ankylosis. Two weeks before discharge, after his improvement had become established, his tonsils were removed as a prophylactic measure. They were found very small and necrotic, and showed *Streptococcus hemolyticus*. This soldier was not making important progress before treatment was undertaken, and the result in this case was not open to question. Further interesting features are described under "Clinical Considerations." He reported himself as doing very well in August, 1919.

Case 23.—C. O'Brien, aged 32, white, orthopedic service, was suddenly affected May 30, 1918, following exposure, with pain, swelling and redness of the right knee and ankle. Foci were reported as negative on admission. Roentgen-ray examination showed bony destruction, spur formation and atrophy. The diagnosis in this case was complicated by the possibility of gonococcal or syphilitic infection and occasional exacerbations due to trauma when drunk. The knee was greatly enlarged, hard, painful on motion, which was limited, but was not very tender on palpation. Rest in a cast achieved much subsidence and some return of function.

Case 24.—Miss S., army nurse corps, aged 48, white, was taken sick in August, 1919, while at Camp Meade, with pains in the hips and the calves of the legs. The nature of her condition was in doubt, but finally it was diagnosed as myositis of a rheumatic nature for which she was referred to U. S. Army General Hospital No. 9. No foci of infection could be detected. There were trifling, almost microscopic overgrowths on the shafts of the phalanges to which only doubtful importance could be attached and the diagnosis of rheumatism or arthritis could not be established. She presented scattered tender points in the legs and gluteal regions and incision over one tibia showed numerous fatty accumulations which were negative on examination and to culture. The sharp contrast of her pain and the normal sugar tolerance first suggested the nonrheumatic nature of this case.

Case 25 (No. 3674).—Eckman, private, aged 29, white. This case was studied as an example of a convalescent arthritic. He had rheumatism in September, 1917, and was in bed for three weeks. Sept. 25, 1918, after exposure, he was acutely affected by swelling, and tenderness of the knees, ankles and calves. Nine teeth were extracted at this time. He began to improve in November, 1918, and was entirely well when discharged Feb. 10, 1919. He had been in bed for ten weeks. On date of sugar tolerance test patient had been well for about eleven weeks. Apparently he had no foci of infection on this date.

Case 26 (No. 3807).—Mosely, private, aged 29, white. This man was studied and reported as a case of convalescent arthritis. He had had no previous attacks of rheumatism. He was taken sick May 14, 1918, following exposure, with pain in the knees, hips, leg and thigh muscles, without swelling. There were foci in the tonsils but he made a recovery without their removal and was entirely well when discharged Feb. 10, 1919. He had been in bed for three weeks and in the hospital for six weeks.

Case 27 (No. 3196).—Sephers Black, private, aged 26, white, had had inflammatory rheumatism at 8 years of age. The present illness began October, 1918, about two weeks after a severe pneumonia, with rheumatic pains in the left leg, then the left shoulder and arm, then both arms and legs. The late

onset after infection is to be noted. He had been practically free from symptoms for five weeks on the date of sugar tolerance test, Feb. 10, 1919. There were foci in the tonsils on this date, and he recovered in spite of them.

CASE 28 (No. 3329).—Fred Stone, sergeant, aged 40, white, had no previous attacks. Following exposure, in February, 1918, he developed arthritis of the spine, shoulders and hips. He had had dysentery in June and August, 1918. His rheumatism did not prevent his continuing on duty in a machine-gun battalion, but about September, 1918, he went to the hospital and never returned to duty. Several teeth were extracted in October because of abscesses and he made a substantial recovery. On the date of the sugar tolerance test, February, 1919, his symptoms had been absent for three weeks.

CASE 29.—C. Collins, aged 27, white, had had since his twentieth year from one to three attacks of rheumatism yearly, involving the knees, hips, shoulders and ankles, without swelling. Present illness began Nov. 9, 1918, following dysentery, and affected the hips, shoulders and knees. He was in bed five weeks, two months prior to the sugar tolerance test made Feb. 10, 1919. Freedom from symptoms had then lasted five weeks. Apparently no foci were present on this date.

CASE 30 (No. 3716).—R. Stewart, aged 26, white, had no previous attacks. September, 1918, following dysentery, there developed gradual swelling and pain of the left knee. He had had abscessed teeth which were not removed, but he made a complete recovery. At the time of the sugar tolerance test, Feb. 11, 1919, he had been well for seven weeks.

CASE 31.—Moehler, aged 34, white, had no previous attacks. Present attack began gradually in October, 1918, and involved the back, hips, thighs, knees and ankles, with swelling. All foci were reported negative and he was well on the date of sugar tolerance test, Feb. 11, 1919.

CASE 32 (No. 3919).—Moon, aged 31, white, had a suggestion of rheumatism in the legs in 1914 and in October, 1918, while in the hospital with diarrhea he was affected with pain and swelling in the knees and ankles. There were apparently no surgical foci, and he had made an entire recovery at time of sugar tolerance test, Feb. 11, 1919.

CASE 33.—G. Cullen, aged 30, white, had no previous attacks. Present attack began gradually, following exposure June, 1918, affecting the right hip, then the left hip, left leg and the shoulders. The teeth showed foci. He took salicylates in large doses overseas, but the condition ran a slow course. He had been practically well for seven weeks when the sugar tolerance test was taken, Feb. 12, 1919. He then had a possible focus in one tooth. No foci were removed in this case and the tonsils had been enucleated twenty-one years before.

CASE 34 (No. 3676).—Gaffney, aged 19, white, had a slight attack of rheumatism in 1915 with "sore joints." The present attack began June 15, 1918, involving the thighs and knees with swelling. He kept with his company until September when he had to go to the hospital and he never returned to duty. There were no demonstrable foci in this case. He was taken sick five months before, and had been well for three weeks prior to the sugar tolerance test, made Feb. 12, 1919.

CASE 35 (No. 3625).—Cabbage, aged 27, white, had no previous attacks. In June, 1919, following exposure, there gradually developed disability in the lumbar spine and the right knee. He made an essential recovery in the presence of foci in the tonsils, which were removed on the day following the sugar tolerance test made Feb. 12, 1919.

CASE 36 (No. 3201).—Clement, sergeant, aged 29, white, had no previous attacks. September, 1918, following dysentery, there gradually developed tenderness and swelling of the knees, feet, ankles and finally all the joints. He made a recovery in the presence of dental foci which were still present on the date of sugar tolerance test, Feb. 17, 1919. At this time his residual symptoms

were chiefly tenderness and pain in the heels on pressure and motion, with some swelling. March 17, 1919, he was practically well and afforded one of the few instances of practically convalescent arthritics still retaining a high sugar curve.

Case 37 (No. 4037).—Chester Tally, aged 19, white, had no previous attacks. Oct. 27, 1918, following exposure, rheumatism began in the right knee, leg and foot, with slight swelling. He went to the hospital and never returned to duty. He recovered in the presence of an abscessed tooth which was not removed and on the date of the sugar tolerance test, Feb. 19, 1919, he had been well for two months. At this time he also had hypertrophied tonsils, which the eye, ear, nose and throat department reported, however, to be free from foci of infection.

Case 38 (No. 4027).—Morris, private, aged 23, white, had no previous attacks. Sept. 27, 1918, he developed pneumonia and was in bed until November 14. Six days after leaving bed his ankles became swollen and painful, followed by disability in the knees, thighs and hips. There were foci in the tonsils, but tonsillectomy was refused as he had recovered by Feb. 19, 1919, the day of the sugar tolerance test. Operation was not insisted on. On this date his freedom from trouble had lasted about three weeks.

Case 39 (No. 4047).—Albert Thompson, aged 25, white, had occasional pains in his feet during the past four years, but no clear rheumatism. About September 21, he developed rheumatism in the right knee which became swollen and painful; he then spent six weeks in the hospital and never returned to duty. There were foci in the tonsils, which were removed after the normal sugar tolerance test on Feb. 19, 1919, on which occasion the right knee had nearly full function and was not tender, but possibly was still slightly enlarged. His state of improvement had then lasted about one month.

Case 40 (No. 4021).—Gross, aged 24, white, had no previous attacks. In September, 1918, he developed pneumonia in France and was in bed three weeks. After recovery, he returned to his work as truck driver. He developed rheumatism early in November in the right ankle; it then spread to the left ankle and knees, which became swollen. He was exposed to cold and wet at the time of onset. He kept at work for two weeks and was then sent to the hospital and was in bed for three weeks. He never returned to duty. This patient had chronic tonsillitis, and on the date of a normal sugar tolerance test, Feb. 20, 1919, he was practically well, three and a half months after onset. His present improvement had lasted one month. No foci were removed.

Case 41 (No. 4184).—Greenberg, private, aged 26, white, had no previous attacks. The onset of his condition, Oct. 20, 1918, followed exposure, and began with pain in the hips and knees. There were apparently no demonstrable surgical foci of infection in the teeth or in the genito-urinary tract; the tonsils were cryptic. He had been well for six weeks by the date of practically normal sugar tolerance test, Feb. 20, 1919.

Case 42 (No. 4001).—Kerr, aged 22, white, had rheumatism in the knees and ankles when 6 years of age. In October, 1918, he had influenza; after recovery he was sent to a replacement camp and did eighteen days of full duty. He was taken sick in December with rheumatism of the knees and ankles. There was a chronic tonsillitis without symptoms, but he made a complete recovery. On the day of the normal sugar curve, Feb. 20, 1919, he had been well for one month.

Case 43 (No. 4194).—Wilburt, aged 40, white, had no previous attacks. Present illness began October, 1918, following exposure, with stiffness, but no swelling, involving the elbows, knees, wrists, ankles and last the feet and fingers On admission symptoms were confined to the fingers, elbows and knees, and on the date of a very slightly elevated sugar curve, Feb. 21, 1919, he was nearly well. His tonsils were removed subsequently and were negative for *Streptococcus hemolyticus*. This relieved trifling residual symptoms.

CASE 44 (No. 4187).—Brake, corporal, aged 20, white, had no previous attacks. Oct. 24, 1918, he developed dysentery which lasted three or four days. While in the hospital, and one week after the attack of dysentery was over, he developed rheumatism of the metatarsophalangeal joints of the feet. The tonsils were positive for foci, and he had made a considerable improvement on admission. Tonsillectomy, March 27, possibly benefited him slightly, but more improvement followed nonspecific protein injections. On the date of a normal sugar tolerance test, Feb. 21, 1919, he presented a tonsillar focus and distinct, but mild, symptoms which had improved and were still improving. The tonsils proved to be diseased slightly.

CASE 45 (No. 4295).—Barger, aged 22, white, had one previous attack in the spring of 1916. He did full duty in the infantry overseas. August 30, pains began in the left knee, hip, ankle, elbow and right shoulder. He remained with his company until October 29, when a rectal abscess developed. An operation was followed by recovery in four weeks. Rheumatic pain continued while he was in the hospital, but became worse after the operation. He never returned to duty but made a slow improvement. In January, 1919, he had an attack of measles in this country with sharp recurrence of arthritis. On admission he presented an intense arthritis of the left hip and the metatarsophalangeal joints of the left foot, the knee being kept flexed in bad position and immovable. This case was of great interest and is described under "Studies on the Blood Sugar." He gave a high curve when seen Feb. 27, 1919, and about one month later, when entirely well, two weeks after tonsillectomy, he gave a normal sugar curve. It is important to note the apparently contributory rôle of the tonsils and the delay of more than six months of invalidism before their removal.

CASE 46.—Hetherington, aged 40, white, had no previous attacks. Present illness began August, 1918, after being gassed and injured in the back. The chief symptom was spondylitis, with changes demonstrable by the roentgen rays. There were foci in the teeth and tonsils. His condition was stationary until after extraction of six teeth, when improvement became marked. He gave a high sugar curve March 6, 1919, and a nearly normal curve six weeks later when the teeth had been extracted.

CASE 47 (No. 4049).—Chaney, aged 29, white, had no clear rheumatism but some knee trouble in 1916. He did full duty carrying a machine-gun tripod, which he thinks induced him to stoop and started the pain and stiffness in the spine and back muscles during August, 1918. In October he developed influenza and was in bed three weeks which was followed by aggravation of his rheumatism. A slow improvement resulted and on admission he was stoop-shouldered and apparently fixed in that position. This case was of much interest and was thought to be tuberculous, but the intercurrence of other rheumatic symptoms in the left knee, hip and shoulder proved its rheumatic nature. He gave a negative reaction to tuberculin. The tonsils were diseased. They were removed with no apparent benefit. Roentgen-ray examination was apparently positive. The lumbar spine was flattened and fixed and there was marked kyphosis in the upper dorsal region. At the time a slightly elevated sugar curve was noted, March 6, 1919, his tonsils had not yet been removed and he was in an interim between exacerbations.

CASE 48 (No. 4238).—Jansen, aged 32, white, had an attack five years before involving the ankles, knees and hips. Present attack began gradually, about May, 1918, involving the back, knees, hips and ankles. Confinement to bed in a sitting position apparently induced a stooping posture which required him to support his body above the waist by placing his hands above his knees. The tonsils had been removed in January, 1919. After admission in February, 1919, after long observation, the patient was found to be improving slowly but steadily, assisted by external measures. A psychic element was suspected but

he gave in the absence of foci an elevated sugar curve. Roentgen-ray examination was negative, but this was probably a true instance of arthritis. This case and the preceding one emphasized the desirability of orthopedic assistance and the difficulty in reaching a correct diagnosis. See "Clinical Considerations."

CASE 49.—Kotschorek, aged 25, white, had no previous attacks. Present attack began Oct. 1, 1918, following injury, with involvement of the lumbar spine, left hip and right knee. This case was on the orthopedic service and proved to be apparently tuberculous. He gave a normal sugar tolerance on two occasions, three weeks apart and the tuberculin reaction was positive. He also had a psoas abscess.

CASE 50.—Lieutenant Gibson, aged 33, white, had no previous attacks. Present attack began in the fall of 1918, involving the left knee and shoulder and later other joints. Tonsillectomy was performed November, 1918, and he had no foci on admission. This case ran a refractory course and gave a moderately elevated sugar tolerance curve which later fell to normal, following nonspecific protein injections. Improvement resulted as described under "Studies on the Blood Sugar" and "Clinical Considerations." The protein injections were accompanied by marked facial herpes.

CASE 51 (No. 3797).—Lau, aged 27, white, had no previous attacks. Symptoms dated from gassing and high explosives Sept. 30, 1918, and were never clearly rheumatic, although possibly truely so. One site of pain was above the costal borders posteriorly; this region was very tender to touch. This was noticed in other patients also. He had eczema of the hands and chronically diseased tonsils. Following an injury in mid-boyhood, one testicle was transplanted with apparently subsequent atrophy. This soldier showed loss of secondary sexual characteristics and grew much fatter in the hospital. He presented a very low sugar curve, that is, a high tolerance. There was probably a mild neurotic element. Tonsillectomy was not followed by noteworthy change.

CASE 52.—Lieutenant Lynch, aged 33, white, had no previous attacks. Present attack began August, 1918, but he recovered. He again became acutely and more severely sick, Oct. 30, 1918, with pains in the feet, knees, right hip, elbow and jaw. He ran a very refractory course and became crippled all over, including the spine and back region. He improved under dietetic measures, and tonsillectomy, as is fully described under "Dietary Considerations." The sugar curve, March 22, 1919, was lower than his clinical condition suggested a priori, but his tonsils proved negative for *Streptococcus hemolyticus*. Subsequent to this test and the tonsillectomy, he developed a severe iridocyclitis but eventually was well started toward recovery.

CASE 53.—Mrs. K., Red Cross worker, aged 47, for some years had various arthritic disability and deformity of all finger joints. She had tonsillar and dental foci March 22, 1919, and gave a high sugar curve. This case was carefully studied and presented several points of interest. Tonsillectomy was performed April 2. Five days later, after two days of sharp unintended low feeding, her hands showed marked improvement. On resuming her full diet the previous condition returned in all its severity. She then developed acute catarrhal jaundice, with extreme obstipation and fecal impaction. During ten days of extremely low diet, necessitated by nausea, her joint condition entirely cleared up again and remained so until she again was eating as before. Her phalangeal arthritis then returned. Dental treatment was postponed until further recovery of strength. She disappeared from observation on closure of the hospital. This case illustrates the definite improvement coincident with postoperative starvation as frequently emphasized by me previously and further exemplified by Case 52 (Lynch). It also illustrates the occurrence of this improvement in the presence of infection (dental foci and probably also infection associated with the catarrhal jaundice). Compare the

improvement of Oberg (Case 22) under low diet in the presence of tonsillar infection as described under "Dietary Considerations." It is particularly to be noted that the arthritis returned twice in her case after twice disappearing under low feeding. (Compare similar return in Case 52, Lynch.)

CASE 54.—Miss A., aged about 59 years, studied by permission of the commanding officer and in conjunction with Lieutenant-Colonel Gittings, had an arthritis of some years standing, affecting her hands. March 26, 1919, she gave a somewhat elevated sugar curve which returned very slowly to its original level. She had been pronounced free from focal infection.

CASE 55.—Cotter, aged 33, white, had no previous attack. Present attack began Nov. 30, 1918, following a hike, with disability in the back, and the right hip, which became stiff and painful to motion and pressure. His symptoms were subacute. He had a tonsillar focus, gave a normal sugar tolerance April 2, 1919, and was apparently not greatly benefited by tonsillectomy or protein injections. There was difficulty in relating his normal sugar curve to his subjective complaints. There were no visible evidences of trouble, but this curve may have been an exception to the usual findings.

CASE 56 (No. 5165).—Kearly, aged 52, white, had no previous attacks. The present attack began Nov. 20, 1918, with pains in the left hip, knee and foot. He walked with much difficulty, and his left big toe showed bony overgrowth objectively and roentgenographically. On admission this patient thought he was improving, following a furlough home, where he received treatment by sweats. He gave a practically normal sugar tolerance and refused tonsillectomy, which was indicated, but he did distinctly improve and finally walked quite freely up and down stairs. When this improvement was fairly established, an abscessed tooth was extracted which may have been of further assistance to his recovery. The normal tolerance of this patient may be another marked exception to the usual findings or referable to the distinct progress toward recovery.

CASE 57.—Longenberger, aged 21, white, had no previous attacks. Present attack began Nov. 27, 1918, in the left knee, following exposure. The course of his disease was very refractory, and he gave a distinctly lowered sugar tolerance. He apparently was free from any foci anywhere, his tonsils having been removed Feb. 5, 1919. This was without any effect May 15. One injection of nonspecific protein had also failed to benefit him. This is one of a number of cases in which reduced diet should have been instituted, but closure of the hospital prevented further treatment.

CASE 58 (No. 5233).—Bruno, aged 21, white, had no previous attacks. Present attack began November, 1918, in the knees and ankles, following exposure. He had positive tonsil and dental foci, but after being in bed one month he made a good recovery and was free from symptoms May 16, 1919, when he gave a moderately elevated sugar curve. No foci had been removed and he had been well for one month.

CASE 59 (No. 5252).—Flanders, aged 27, white, had inflammatory rheumatism when 13 years of age, and very slight pains in January, 1918, but he was not confined to bed. A bad tooth was extracted two years previously. Present attack began Nov. 15, 1918, with stiffness and pain in the legs, ankles, feet, left shoulder and hips, with swelling of the feet but no fever. He was in bed one month and on admission had made a considerable recovery, but the heels under the Achilles tendons were very tender to pressure and motion. He thought his condition was stationary for six weeks past. He gave a sugar tolerance definitely but not markedly below normal, the curves showing a tendency to remain elevated.

The roentgen-ray examination was positive, and he had foci in his teeth and tonsils. Closure of the hospital prevented final data in this case, but he was evidently on the way to recovery. There was no removal of foci.

Case 60 (No. 4804).—Herron, sergeant, aged 24, white, no previous attacks. Present illness began May, 1917, following appendiceal abscess with pain in the hips, fingers and knees. Following a sharp exacerbation about May 15, 1919, accompanied by fever, as described under "Clinical Considerations," he gave a greatly lowered sugar tolerance, although at that time he was free from symptoms. He had been treated by acetylsalicylic acid but had received none on the day of the test. In the early course of the present illness he had been benefited by treatment at Hot Springs, Ark. Repeated examinations made at U. S. Army General Hospital No. 9 failed to reveal demonstrable foci. Closure of the hospital prevented further observation.

Case 61 (No. 5313).—Harry Miller, aged 22, white, had slight rheumatic pain in the left leg three years previously. Present attack began April, 1919, with disability in the heels and in the right knee. He was admitted from his command and while in the hospital he developed a sharp exacerbation with fever, pain and swelling. He had foci in the tonsils, which were removed April 29. Eight days previously, during this exacerbation, he showed a very high sugar curve, which was still high three days later when his symptoms were relieved by acetylsalicylic acid. Twelve days after the tonsillectomy he had another sharp exacerbation, with fluid in the right knee and pain in the neighboring muscles. May 13, two weeks after the tonsillectomy, and when convalescing from the exacerbation just mentioned, he gave a much lower sugar curve, indicative of a marked return of the sugar tolerance toward normal, although it was still slightly elevated, to 0.167 per cent. Closure of the hospital prevented following this case further.

Case 62.—McKensie, aged 20, white, had rheumatic fever when 10 years old, another attack in 1918, and three other mild attacks thereafter, five attacks in all. This case is described under "Observations on the Blood Sugar" as an instance of ma . dly lowered sugar tolerance during rheumatic fever. He had a dental focus. After recovery from the inflammatory attack, for which he was admitted, he again developed an attack with fever. He refused dental treatment, but recovered symptomatically under medication and was discharged on the closure of the hospital. He gave a double plus Wassermann reaction (army standard).

Case 63 (No. 4919).—Folden, aged 24, white, for ten years had been subject to arthritic pains in the right leg. Present illness began gradually in June, 1918, in first the right leg and arm later involving the elbow and shoulder, following exposure. This soldier had really never been well since his induction into the army, although he recovered sufficiently overseas to receive a gunshot wound going over the top. He illustrates the type of person who should be rejected in the draft or preferably segregated for removal of disease producing factors. He had tonsillar foci of infection which were removed April 24 as he was still invalided then. May 12, eighteen days later, he had a sharp exacerbation of his symptoms, with enlargement and tenderness of the leg, simulating phlebitis. This is described under "Clinical Considerations." Closure of the hospital prevented further observation.

Case 64 (No. 3689).—Harry Fisher, aged 23, white, one month before entering the army had rheumatism in the elbow, shoulder, fingers and ankle. Present attack began December, 1918, following exposure in the trenches and affected his feet and hands. There were foci in the tonsils and positive roentgen-ray findings. On admission he had made a limited improvement, but later he developed a severe rheumatic iridocyclitis because of which tonsillectomy was postponed. Shortly thereafter he disappeared from observation on closure of the hospital.

Case 65 (No. 5245).—Gale, aged 28, white, had no previous attacks. Present attack began Sept. 15, 1918, about coincidentally with an abscess of jaw following tooth trouble and affected his right leg, hip and knee, and later

his hands. He was much benefited by warm baths at Aix and made a considerable recovery in the presence of a tonsil focus. This was later removed with much further benefit.

Case 66.—Basits, aged 20, white, was taken sick overseas with trouble in his left ankle which later was incised. After improvement his left knee grew painful, it became very large and fluid accumulated in it. It was regarded as tuberculous but repeated guinea-pig injections overseas and in this country proved negative. Tuberculin injections caused a marked febrile rise and made him distinctly worse. Dental and tonsil foci were removed without obvious improvement. After applying a cast, the condition subsided somewhat. Closure of the hospital prevented further observation. This case illustrated that cases may strongly suggest tuberculous conditions without being so. Other instances of the kind indicated that tuberculous arthritis may not be as frequent as has been supposed.

Case 67 (No. 3550).—Burgess, corporal, aged 23, white, had no previous attacks. He had dysentery in August, 1918, lasting seven days. It never recurred. He spent one week in a convalescent camp and then suddenly developed rheumatism of the right wrist, left hip and both knees. He was in bed two and one-half months. This case illustrates the occasional late onset following infection described under "Clinical Considerations." Convalescence was slow but practically complete. The tonsils had been removed when he was 12 years of age. This case apparently ran its entire course in the absence of demonstrable surgical foci.

Case 68.—Lieutenant Turner, aged 31, white, had one previous attack in 1917. Present attack began gradually about Sept. 1, 1918. About October 25 he reported sick, with involvement of his ankles, feet, elbows, shoulders and knees. Tonsillectomy was performed Feb. 18, 1919, when he had recovered except for involvement of one knee. Only limited improvement followed, and protein injections were necessary two months later. These helped slightly. On discharge, his condition was only intermittently active.

Case 69 (No. 4481).—McIntyre, sergeant, aged 21, white, had no previous attacks. While in a German prison camp he developed "meningitis," Oct. 1, 1918. Following recovery he had stiffness and tenderness in the back, with some symptoms in the left wrist. He had foci in his teeth and tonsils and tonsillectomy was performed April 9, 1919. One tooth was extracted. Diminished tenderness was noted five weeks later; he also had marked flatfoot from invalidism. The back was flattened over the lower half, and this case constituted one of the dorsal type difficult of diagnosis. The tonsils were negative for *Streptococcus hemolyticus*.

Case 70 (No. 3809).—Fontanella, aged 20, white, had no previous attacks. Present attack began gradually in October, 1917, following exposure. He remained on full duty until March when he was put on light duty. May 24 he was sent to the hospital. This man presented a wide female type of pelvis. He was taken sick in the presence of tonsillar and dental foci. One tooth was extracted about April 1. Two tuberculin tests were negative. His chief complaint was dull pains in the left leg and later in the back. A mass was palpable to the left of the vertebral column posteriorly; diagnosis apparently was Pott's disease. His function improved much after application of a brace. This case illustrates the difficulties of diagnosis, unless qualified orthopedic help is available.

Case 71 (No. 4567).—Crawford, corporal, aged 30, white, had one attack in 1913 in his hip. Present attack began in September, 1917, following exposure. Tonsillectomy was performed the same month without benefit so far as the mild symptoms were concerned. The distribution was left hip, right ankle, back and occasionally other joints. The arthritis grew worse in October. In January, 1919, he had a tooth extracted, also without benefit. This case was

very severe. The man became bed-ridden and developed edema of the ankle. He was too sick for radical treatment and on closure of the hospital he was transferred to Hot Springs, Ark.

Case 72.—Barkely, aged 27, white, had no previous attacks. He had tonsillitis in November, 1917, erysipelas in January, 1918; pleurisy in March, 1918; pericarditis in April, 1918; mild ear trouble in August, 1918, at which time the wrist became involved. The wrist grew worse in December, 1918, with swelling and some tenderness and a heel ulcer developed in January, 1918. The fluid contents were sterile. The ulcer refused to heal and the wrist made little or no progress. Tuberculosis was a strong possibility, but was not proved. This case had tonsillar and dental foci which were removed. The Wassermann test and roentgen-ray examination were negative. On the orthopedic service.

Case 73.—Lieut. Jordan, aged 23, white, had no previous attacks, but had frequent attacks of tonsillitis during last two years. Present attack began in the right hip, right sacroiliac joint and lower lumbar vertebrae about Sept. 1, 1918. Tonsillectomy was performed April, 2, 1919. He improved but was still greatly disabled. Further observation was prevented by closure of the hospital. This case illustrates the repeated delay observed in instituting the proper therapy.

Case 74 (No. 5351).—Curley, aged 32, white, had no previous attacks. The present attack began about Feb. 1, 1918, involving the legs, back, hips, knees, ankles, right shoulder and neck following exposure. Tonsillar and genito-urinary foci were present. He was apparently improved by prostatic massage. Tonsillectomy was performed April 12, 1919.

Case 75 (No. 4828).—Dion, sergeant-major, aged 30, white, had no previous attacks, but he had a sore throat nearly every year. Present attack began in January, 1918, with pains in the knees and feet, following exposure. His tonsils were removed March 24, 1919, and he also had a dental abscess. This case resembled Case 10 (Masood), Case 14 (Lowe), and Case 15 (Studebaker) in the exquisite tenderness on light touch over the legs and feet, and absence of objective evidences. Closure of the hospital prevented final observation.

Case 76.—Miss H., aged 45, army nurse corps, had no previous attacks. She was taken sick suddenly Jan. 1, 1919, with rheumatism of the left shoulder and right hand. On admission her chief trouble was in the right sciatic region and in the left shoulder. She was reported definitely to have no foci of infection and after remaining stationary for some months she showed marked and gratifying improvement under restricted diet as detailed under "Dietary Considerations." A genito-urinary examination was not made.

Case 77 (No. 5443).—Lieutenant Morris, aged 24, white, had no previous attacks. He was taken sick in August, 1918, with involvement of his left hip and later the left foot, both knees, hips and shoulders and one finger. He had dental, tonsil and genito-urinary foci. An abscessed tooth was drained without benefit in September, 1918. March 27, his tonsils were removed with good results and he received treatment for prostatitis. Six weeks later he was better but he was not well on closure of the hospital.

Case 78 (No. 4997).—Kirkwood, aged 23, colored, had no previous attacks. December, 1918, he developed rheumatism of the ankles, knees, right hip, right wrist and back. He was in bed three weeks with fever, much swelling and pain. He had a gonococcal infection in August, 1918. The only infection was located in the genito-urinary tract and this case may have been of gonococcus origin, although this is uncertain. He had made considerable improvement along expectant lines and was further benefited by genito-urinary treatment but was not well on the closure of the hospital.

Case 79.—Cox, aged 36, white, had no previous attacks. He had rheumatism of several joints following exposure in the trenches, and was struck on the wrist with a musket Feb. 21, 1918. He then became stiff in every joint within a few days. All symptoms subsided, except in the wrist. On

admission he was found to have a fracture of one carpal bone. Removal of fragments and immobilization was followed by improvement and eventual subsidence, leaving a small range of motion. The reaction in the wrist following operation, however, was atypical and was regarded by Major Cleary of the orthopedic service as due to a rheumatic condition. There was undoubtedly some slight rheumatism elsewhere. He had foci in the tonsils.

Case 80 (No. 4479).—Spaterro, aged 32, white. No previous attacks. Present attack began in August, 1918, with pains in the left wrist which became swollen. He went to the hospital in November and remained there. The roentgen ray showed one carpal bone to be markedly rarefied. There were no foci anywhere. The case was thought to be tuberculous but a negative tuberculin reaction was obtained. This seems to be an atypical example of true arthritis. A cast was advised when the hospital closed and he was transferred elsewhere.

Case 81 (No. 3312).—Schoonover, aged 24, white, had no previous attacks. He did full duty in the infantry until he was gassed in August and sent to the hospital. He had been exposed to cold and wet before then, and had stiff joints as a result. In October, however, he was for the first time seriously afflicted with rheumatism which came on while in the hospital, first involving the right hip and right knee, then both shoulders. He was in bed October and November, then improved, but the right knee remained in statu quo with some symptoms at other points occasionally. He had a tonsillar focus which was removed although no marked influence could be seen on the arthritis in two and one-half months.

Case 82.—Lieutenant Keys, aged 33, white, had rheumatism in 1914 and 1916. Present attack came on Jan. 2, 1919, involving the right shoulder, back, knees and other joints. He had foci in the genito-urinary tract and tonsils. When considerable improvement had occurred, tonsillectomy was performed. He continued to improve further and also received treatment for the genito-urinary condition. The tonsils were negative for *Streptococcus hemolyticus*. This case was regarded by Capt. George Smith, chief of the genito-urinary department, as one of the few cases apparently due to genito-urinary infection. His further improvement seemed to relate somewhat to treatment of this.

Case 83.—Mrs. G., aged 50, white, was studied by permission of the commanding officer. She had suffered for some years with a progressive arthritis of her hands, knees, shoulders and feet. She had her tonsils and all other foci removed two years before without any real benefit.

Case 84 (No. 1275).—DeKim, sergeant, aged 42, white, had no previous attacks. Present attack began gradually in January, 1918, involving the left shoulder, hip, knee, ankle and spine, following exposure. The knuckles of the hand were enlarged and headache was a persistent symptom. Received frequent protein injections without benefit.

Case 85.—Leeman, aged 18, white, had no previous attacks. Present attack began in October, 1917, involving the feet, following exposure. Several teeth were extracted in France. Had foci in his tonsils which were removed and found diseased. This man had great tenderness in the metatarsophalangeal joints of the feet, and had not been able to walk for a year. By the date of tonsillectomy he had greatly improved but this operation benefited him further. The loss of time in this case and the propriety of tonsillectomy a year sooner are to be noted.

Case 86.—Zuch, aged 28, white, had no previous attacks. Present attack began in April, 1918, with pain and redness of the hip, knee and shoulders, following exposure and injury to the left hip. His case ran a chronic course. He recovered except for the left hip and knee. A small fracture in the head of left femur was found. The roentgen ray gave definite evidence of arthritis elsewhere. No foci were detected although the tonsils were submerged and may have constituted foci.

CASE 87.—Sharpe, aged 47, white, had previous trouble in his back. Present attack began in March, 1918, involving sacroiliac region, following exposure to damp. He had abscessed teeth and was discharged with mild disability shortly after the inauguration of the arthritic service. He was instructed to have the offending teeth removed.

CASE 88.—Bartkiavicus, aged 26, white, had one attack in 1914. Present attack began in July, 1918, involving the right shoulder, left ankle and hips, following gas poisoning. He had tonsillar foci which were removed Dec. 13, 1918, after he had made a full recovery.

CASE 89.—Cichon, aged 22, white, had had slight recurrent attacks. Present attack began July 29, 1918, in the wrists and hands, following exposure. He had foci in his teeth but made an essential recovery before their removal.

CASE 90.—Mulledy, aged 21, white, had rheumatism for three years at intervals. Present attack began in September, 1918, in the left ankle, knee, hip, shoulder and elbow. Most of these joints were red and swollen. A tonsillectomy was done Nov. 1, 1918, and was followed by slow improvement. On discharge, January 2, his symptoms were trifling and intermittent.

CASE 91.—Saxton, aged 24, colored, had had no previous attacks. The present attack involved the knees and ankles. There was apparently no focus and he was treated with repeated vaccine injections with alleged good results.

CASE 92.—Kolden, aged 26, white, had an attack in 1910 lasting eight months. Present attack began acutely Nov. 21, 1917, in the knees, ankles, back and right hand. Tonsils and a root abscess were removed without marked benefit. History incomplete.

CASE 93.—Hamburger, aged 23, white, had no previous attacks. Present attack began January, 1918, following exposure. He improved and then relapsed in May, 1918, many joints and his back being affected. He had foci in tonsils and teeth and had convalesced considerably when admitted except for slight tenderness in the left hip and knee. Removal of foci was followed by disappearance of residual symptoms and this soldier was still well in June, 1919.

CASE 94.—Meadors, aged 23, white, had no previous attacks. Present attack began Jan. 14, 1918, in the wrists, elbows, hips and shoulders. He had foci in his tonsils which were removed Sept. 28, 1918. In February he had made slight progress, but had many painful joints in his hands. He was further improved by nonspecific protein injections and was discharged about well.

CASE 95 (No. 4901).—Tingue, aged 27, white, had a previous attack when 14 years of age. Present attack began in August, 1918, overseas during an attack of dysentery. The knees and later the hips and left shoulder became involved, and he made a slow and limited improvement. He had foci in his tonsils which were removed May 7, 1919. At closure of the hospital, June 1, the elapsed time did not permit of reliable data as to his progress. See "Clinical Considerations," Part V.

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A RESEARCH ON BLOOD SUGAR IN DEPANCREATIZED DOGS *

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Recent experiments on the intravenous injection of epinephrin in normal dogs give rise to a question of considerable interest. If the injection of epinephrin causes a temporary hyperglycemia in normal animals, the blood sugar increasing shortly after injection, what would be the result in animals from which the pancreas has been removed? On this idea of investigation, these series of experiments were commenced. The intravenous injection of epinephrin in man has shown, in addition to a temporary hyperglycemia, in some cases a decrease in the output of carbon dioxid from the lungs, which supports the theory that epinephrin inhibits the combustion of sugar in the body, in opposition to the school that believes epinephrin increases the blood sugar by increasing the output of glycogen from the liver. At least, it seemed probable in undertaking this work that a relationship or antagonism might be determined between the pancreas and epinephrin toward the metabolism of the sugar in the body.

My procedure in carrying out a number of experiments to this end was to depancreatize completely a dog and inject a given amount of epinephrin several days after operation; after injection withdrawing the blood at regular intervals, from four minutes to one hour, for the purpose of the blood sugar determination.

The method of removing the pancreas was one of dissecting it away from the mesentery in which it is enveloped. It is not difficult to ligate the minute vessels leading to the gland from the duodenal artery and vein, which can be dissected out carefully without destroying the circulation to the duodenum, and at the same time all the surrounding pancreatic tissue separated from them intact with the pancreas. At least one layer of mesentery can be preserved, except a small area about 3 cm. in diameter, where the pancreatic duct enters the duodenum. However, the preservation of a large portion of the duodenal mesentery seems to be of little importance, as adhesions will form about the duodenum. In a satisfactory number of dogs, the adhesions did not interfere with the function of the intestine, or cause obstruction, waiting a sufficiently long time after operating before following out the experiments.

* This work was done in the laboratory of Prof. C. Achard with Mm. A. Ribot and Leon Binet, whom I thank for their council in the work.

The greatest difficulty encountered in removing the pancreas was in the region of the splenic artery and vein, where, in order to avoid hemorrhage, there is danger of leaving a small portion of the gland.

Six dogs were operated on for removal of the pancreas by the method described above. Two died from postoperative hemorrhage, one twenty-four hours, the other forty-eight hours after operation. One animal died three days after operation, owing to obstruction from adhesions formed about the duodenum.

If any pancreatic tissue is left behind, the blood sugar is certain to give indication of the error. One dog (B) forty-eight hours after operation showed a blood sugar of 2 gm. per thousand c.c., and two days later when the blood was withdrawn for examination it showed approximately a normal sugar content (1 gm. per thousand c.c.). This animal was killed twenty-one days after operation. Dense adhesions were found in the region of the pylorus and duodenum. In spite of the adhesions, the duodenum had functioned well. For fifteen days the dog had been eating the usual diet of meat, stew and rice. At necropsy a search was made for pancreatic tissue, and after a prolonged examination a small piece of tissue, not exceeding in size half that of a hazel nut, was found in the region of the postmesenteric glands. Two other dogs that were operated on continued to show a hyperglycemia. One of these animals (Dog A) died the tenth day after operation, and the other (Dog C) was killed twenty-four days after pancreatectomy. No pancreatic tissue could be found in either of these animals at autopsy.

Those animals from which nearly all of the pancreas is removed, usually showed a hyperglycemia the first two or three days after operation. They may be useful in that time to observe the effect of intravenous injection of adrenalin upon the blood, but not after the blood sugar has returned to normal, as we then have quite the same condition as in normal dogs. In Dog B (Table 1) we have an example of this, as four days after operation the blood sugar was normal, and incomplete removal of the pancreas was found at necropsy. Two days after operation the blood sugar was double the normal amount. It does not concern this particular work whether the small amount of pancreas left in the body was insufficient, together with the shock of the operation, for the first couple of days, to take over the glycogenetic function of the pancreatic tissue removed, or whether in a few days the remaining pancreatic tissue hypertrophied sufficiently to take up the glycogenetic function of the pancreas. But it is quite certain that the hyperglycemia existing in dogs up to the time of their death, from ten to twenty-four days after operation, was not due to the operation

per se, but to an absolute removal of the pancreas, as sufficient time had elapsed for any remaining tissue of the gland to reestablish its function.

As will be seen in Table 1, in the normal dog (Dog A) there was a marked rise of sugar in the blood, after the intravenous injection of epinephrin. Whether epinephrin inhibits the metabolism of sugar in the body or tissues, or whether it augments the output of glycogen from some organ is of great interest, but difficult to determine absolutely. The decrease in the output of carbon dioxid after the administration of epinephrin is injected in man speaks strongly for the increase in blood sugar being due to an inhibition on the part of epinephrin to the burning of the sugars in the tissues.

TABLE 1.—RESULT OF INJECTION OF EPINEPHRIN IN NORMAL AND DEPANCREATIZED DOGS

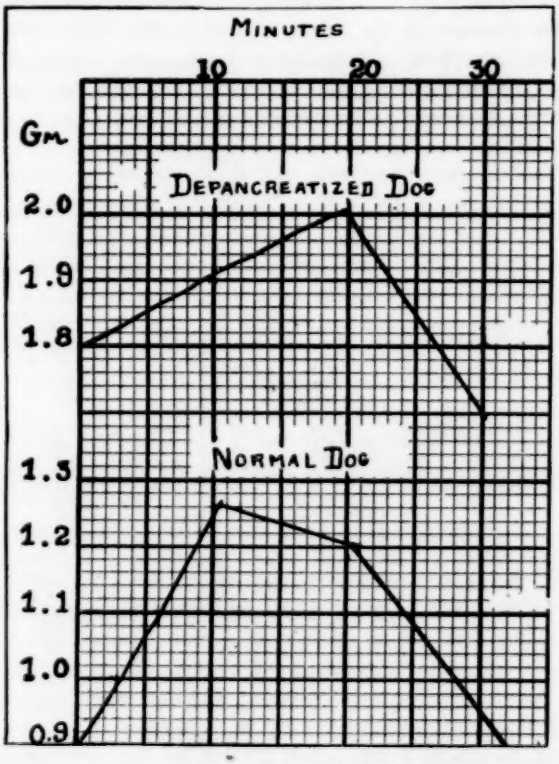
Dog		Amount of Epinephrin Injected	Blood Sugar, Gm. per 1,000 C.c.				
			Before Injection of Epinephrin	Minutes After Injection of Epinephrin			
				10	20	30	40
A	Before depancreatization	1 mg.	0.95	1.25	1.20	0.95	
A	After depancreatization	1 mg. 1 day after operation	1.80	1.90	2.00	1.65	1.55
B	After depancreatization	2 mg. 4 days after operation	1.00	1.30	1.50		
C	After depancreatization	2 mg. 11 days after operation	3.00	3.00	3.00	3.10	

In Dog A the rise of blood sugar after epinephrin injection proportionately was not as great after depancreatization as before, and the fall to the previous sugar level was more abrupt than in normal dogs. This can plainly be seen by a comparison of the two curves. We also see the rise in blood sugar of the dog when depancreatized was much slower after injection than in a normal dog.

In Dog B, where a very small portion of the pancreas had been left in the animal, the rise in blood sugar after injection was quite similar to that of a normal dog.

In Dog C the injection of epinephrin after operation had practically no effect on the blood sugar. There was not any rise in the blood sugar observed in this depancreatized dog, as in the normal animal. One would suppose that if epinephrin inhibits the metabolism of sugar in the tissues in normal dogs it would do likewise in depancreatized dogs, and thus produce a higher blood sugar, by allowing sugar to pass into the circulation unburned. But in depancreatized dogs there

is a constant hyperglycemia, showing by our experiments very little or no rise by the injection of epinephrin. By removal of the pancreas, it seems quite possible that something has been removed favorable to the combustion of sugar in the body, and in depancreatized dogs the blood sugar is increased permanently in the way that it is increased temporarily after injection of epinephrin in normal dogs. The sugar



Blood sugar in grams per thousand cubic centimeters after injection of 1 mg of epinephrin.

is passing into the circulation unburnt, as the influence favorable to the combustion of the sugar has been removed. If in depancreatized dogs, sugar passes into the circulation and is not broken down by the tissues, then epinephrin by injection can have no further action in inhibiting the metabolism of the sugars and be capable of producing much of a rise in blood sugar. It would seem that the pancreas has

exactly the opposite effect of epinephrin on the metabolism of the sugars in the tissues, the pancreas augmenting, the epinephrin inhibiting.[1]

Dogs injected with sugar intravenously show some difference before and after depancreatization in the rapidity of reducing additional sugar added to the blood.

TABLE 2.—FIVE GM. OF GLUCOSE IN SOLUTION INJECTED INTRAVENOUSLY

	Blood Sugar, Gm. per 1,000 C.c.					
	Before Injection	Minutes After Injection				
		10	20	30	40	50
Normal dog	1.15	1.35	1.15	1.15	1.15	
Depancreatized dog 48 hours after operation.	2.00	3.00	2.6	2.7	2.45	2.35

In each case, that of the normal and depancreatized dog, the tables show the result in blood sugar expressed in gm. per thousand c.c. after equal amounts of glucose have been injected. The dog without pancreas had a slower fall in blood sugar than the normal animal. In other words, the normal dog showed a greater ability to handle the added amount of sugar than the dog without the pancreas. If the pancreas did not play a part in the metabolism of sugar in the body we would expect the blood sugars after the injection of glucose to fall to their former respective levels with about the same rapidity. If the glycogenetic function of the pancreas was merely to control the output of glycogen from the liver, the removal of the pancreas ought not to interfere with the handling of an added amount of sugar to the blood. But Table 2 shows that the fall in blood sugar to the level before injection is not as rapid as in the depancreatized dog.

SUMMARY

1. Complete removal of the pancreas produced a permanent hyperglycemia, and any part of the pancreas left in the animal after operation later manifested itself by a fall in blood sugar.

2. Epinephrin by intravenous injection in normal dogs increased the blood sugar. With the pancreas removed, epinephrin produced

1. It may be possible in life that the pancreas acts as a check on the output of epinephrin from the suprarenal glands, and that with the pancreas removed there is an excessive production of suprarenal secretion put out into the circulation, thus inhibiting the metabolism of the sugars and allowing them to pass unburnt into the circulation. Examination of the suprarenals of one person dying with diabetes and two depancreatized dogs showed a very low epinephrin content by the Folin colorimetric method for quantitative examination of epinephrin. J. Exper. Med. **19**:536, 1914.

very little, if any, change in the blood sugar. Under this condition, as a possible explanation, sugar is passing freely into the circulation unburnt, and therefore the epinephrin can have very little further effect in increasing the blood sugar by inhibiting sugar metabolism.

3. It is reasonable to believe that the pancreas produces some substance which favors the metabolism of the sugars in the tissues, as sugar injected intravenously is not handled as readily in the depancreatized animal as in the normal dog.

THE PROGNOSTIC VALUE OF CHOLESTERINEMIA IN CHRONIC NEPHRITIS

FINAL REPORT

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In a preliminary report on this subject,[1] I presented a number of cases to show that a hypercholesterinemia is usually to be found in cases of chronic nephritis which are progressing favorably, and that a normal or subnormal figure for the serum cholesterol, in cases of chronic nephritis, is of distinct prognostic importance and value. The measure of cholesterinemia in the cases enumerated in my early paper accurately foretold the prognosis in individual cases.

The study of the chemistry of the blood has made giant strides during the past few years, and we are now enabled to measure accurately, especially the nonnitrogenous constituents of the blood — total nonprotein nitrogen, urea nitrogen, creatinin, uric acid and sugar. There seems to be little disagreement as to the best quantitative methods to employ, and the clinician has a right to accept the quantitative determination without a doubt.

Much work along this line has been done, but notably in nephritis and diabetes mellitus, conditions in which the carbon dioxid combining power of the blood is of exceedingly great value from a prognostic standpoint.

While there is no doubt that the study of the prognosis in chronic nephritis must, of necessity, be associated closely with those chemical metabolic products which the kidneys normally excrete, and which, in the event of functional decompensation, are excreted with increasing difficulty, resulting in a corresponding increase of these same substances in the circulating blood, there is evidence to show that the uremic death of nephritics is due to a severe acidosis. The marked fall in the carbon dioxid combining power of the blood in uremia is a striking proof of this, and it has been my belief for many years that the lipoid substances of the blood are intimately associated in the chemistry of acidosis.

With the advent of so-called "blood chemistry," investigators actually plunged into the study of chronic nephritis with exceedingly valuable results. I have always insisted, however, that the study of cholesterinemia in chronic nephritis was equally as important, if not more

1. New York State M. J. **15**:300 (Aug.) 1915.

so, in an endeavor to prognosticate in any given case. The work begun in 1914 was, therefore, continued. It is my purpose to show how intimately associated are the study of the cholesterinemia and the study of the nonnitrogenous products of the blood in chronic nephritis, and at the same time, to add further weight in substantiation of my preliminary report on the subject.

Reference to the preliminary report will show that the measure of cholesterinemia in the individual cases presented foretold the prognosis very accurately in each case. It is to be remembered that the cholesterinemia must be interpreted properly in each case, and allowances must be made for any coincident clinical conditions that experience has taught us tend to increase or decrease the amount of cholesterol in the blood. The early report showed that a hypercholesterinemia is present in all cases of chronic nephritis, and that the measure of cholesterinemia decreases as the uremic state is approached. All cases of uremia, and all cases terminating fatally in coma, showed a most decided hypocholesterinemia.

Since the introduction of blood chemistry, the functional ability of the kidneys has been studied in terms of the retention in the blood of the total nonprotein nitrogen, urea, creatinin and uric acid, and the carbon dioxid combining power of the blood serum. Our studies have shown that evidence of increasing retention in the blood of the products just enumerated is of prognostic importance, and rather accurately foretells an impending uremic state.

The blood figures generally recognized as being the normal for the blood constituents enumerated, are as follows:

Total nonprotein nitrogen, from	25	to	35	mg. per hundred	c.c.
Cholesterol, from	1.50	to	1.80	gm. per thousand	c.c.
Urea nitrogen, from	12	to	18	mg. per hundred	c.c.
Uric acid, from	0.8	to	2.5	mg. per hundred	c.c.
Creatinin, from	0.8	to	2	mg. per hundred	c.c.
Sugar as glucose, from	0.08	to	0.15	per cent.	

Any increase in the figures mentioned is to be regarded as evidence of retention of these products, but in speaking of cholesterol, it is probably not correct to speak of it as being retained, for, in the normal individual it is not a product of excretion. When figures as high as 80 mg. of nonprotein nitrogen per hundred c.c. of blood are obtained, a very definite evidence of retention of these waste nitrogenous products is indicated. When figures as low as 1 gm. of cholesterol per thousand of blood are obtained, they are distinctly below normal, especially in a condition where a decided increase is to be expected. It is just this normal, or subnormal figure for the cholesterol in chronic nephritis, which is of such interest and importance.

REPORT OF CASES

The following cases will show the prognostic import that can be attached to the measure of cholesterinemia in chronic nephritis.

CASE 1.—Male, aged 66; no jaundice; no fever; moderate arteriosclerosis; blood pressure, 220; Wassermann reaction, negative; urine contained albumin, hyaline and granular casts. The general condition of the patient was not very good at the time the blood was examined. Examination of the blood showed: urea nitrogen, 55 mg.; uric acid, 2.7 mg.; creatinin, 1 mg., and sugar 0.132 per cent., while the cholesterol was 2.05 mg.

Under the clinical circumstances one would expect a much higher cholesterol figure. The absence of a decided hypercholesterinemia in this case should make me suspect a moderate degree of retention, and the figures for the nonnitrogenous products indicate that retention.

In presenting these cases, only relevant clinical states, as they influence cholesterinemia, are recorded. These clinical states are the following: (1) Fever reduces cholesterinemia; (2) jaundice increases cholesterinemia; (3) arteriosclerosis (active) increases cholesterinemia.

CASE 2.—Female, aged 60; temperature, 100.8 F., no jaundice; slight arteriosclerosis; urine contained albumin, hyaline and granular casts; no edema; eye grounds negative; Wassermann negative. At the time the blood was examined, there were no symptoms suggesting an impending uremic state, but the cholesterinemia amounted to only 1.73 mg., a hypocholesterinemia under the circumstances. On the following day, a sudden delirium set in, the patient gradually went into coma and died two days later.

In this case, while there are no additional blood figures, I am reasonably sure that examination would have shown evidence of a decided retention of waste nitrogenous products.

CASE 3.—Female, aged 59; was admitted to the hospital with a diagnosis of carcinoma of the stomach, although repeated roentgen-ray examinations failed to substantiate that diagnosis. The temperature was 98 F.; the Wassermann reaction was negative; hemoglobin, 52 per cent.; red blood corpuscles, 2,420,000; leukocytes, 9,200, polymorphonuclears, 66 per cent.; no jaundice; urine showed evidences of nephritis.

Our attention was drawn to her when she began to vomit and became drowsy, although previous to this, the patient manifested no signs of an impending uremia. The blood figures were as follows: Cholesterol, 1.65 mg.; nonprotein nitrogen, 1.25 mg.; urea nitrogen, 100 mg.; uric acid, 5.5 mg.; creatinin, 13.4 mg.; sugar, 0.129 per cent.; carbon dioxid, 10 volumes per hundred c.c.

These figures certainly suggest a threatened uremia. The stupor continued, coma supervened and the patient died at the end of two days.

CASE 4.—Male, aged 50; admitted to the hospital with a diagnosis of chronic nephritis; no jaundice; temperature, 99 F.; Wassermann negative; blood pressure, 180, moderate arteriosclerosis; urine contained albumin and hyaline and granular casts; no edema; general condition good. The following figures were obtained: Phenolphthalein elimination, 79 per cent.; urea nitrogen, 17.5 mg.; uric acid, 1.4 mg.; creatinin, 1.5 mg.; blood sugar, 0.09 per cent., and cholesterol 2.34 mg.

Having done well, the patient was discharged, but returned to the hospital a year later. On his second admission, he was restless, noisy, not mentally clear, had a motor aphasia, was drowsy and sleepy, but showed no convulsions. His blood pressure was 170/110; no jaundice; no fever; urine contained albumin and hyaline and granular casts.

We were here dealing with an undoubted case of threatened uremia, and the blood figures obtained verified the condition. They were: nonprotein nitrogen, 110; urea nitrogen, 58; creatinin, 3.5; uric acid, 5 mg. and sugar, 0.136 per cent., with a carbon dioxid combining power of 42 volumes per hundred c.c. The cholesterinemia amounted to 1.43 mg., a decidedly low figure, under the circumstances.

Two weeks later the general condition of this patient was somewhat improved, but at the end of another week, the general condition again became worse and the following blood figures were obtained: nonprotein nitrogen, 41 mg.; urea nitrogen, 16 mg.; uric acid, 1 mg.; creatinin, 1.1 mg.; sugar, 0.146 per cent.; carbon dioxid, 48.5 volumes per hundred c.c. These are practically normal figures, but the cholesterinemia continued low, 2.02 mg. Subsequent work was not done in this case, but the patient, after some ups and downs, eventually died in uremic coma.

Case 5.—Female, aged 61; was admitted to the hospital with a mild chronic nephritis and arteriosclerosis; no jaundice; no fever; blood pressure, 210; Wassermann, negative; urine, very faint trace of albumin and no casts. Eyegrounds showed neurochorioretinitis. A facial palsy, with a pure motor aphasia, justified the diagnosis of hemorrhage from the middle meningeal or middle cerebral artery.

The blood figures in this case were as follows: Urea nitrogen, 16 mg.; uric acid, 2.7 mg.; creatinin, 1.5 mg.; sugar, 0.106 per cent., and cholesterol, 2.93 mg. These figures certainly do not suggest a severe chronic nephritis. Four days later, a sudden coma developed and the patient died. Death was most likely due to cerebral hemorrhage.

Case 6.—Male, aged 52; a case of chronic nephritis with undoubted uremic state, for when the blood was first examined the patient was in coma. Quantitative estimations of the nonprotein nitrogenous constituents of the blood at that time gave the following: Urea nitrogen, 35 mg.; creatinin, 1.3 mg.; sugar, 0.112 per cent., and carbon dioxid combining power, 31 volumes per hundred c.c., figures that surely do not indicate a very severe retention. There was no jaundice; blood pressure was 150; no edema and the urine showed albumin and hyaline and granular casts. The cholesterinemia amounted to 1.77 mg. a decidedly low figure under the circumstances. With sodium bicarbonate infusions the patient held his own for a few days, but a second examination of the blood failed to show the apparent gravity of the condition. The figures obtained were as follows: Urea nitrogen, 31; uric acid, 2.3; creatinin, 2.5; sugar, 0.12 per cent.; carbon dioxid combining power, 48 volumes. Ten days later the patient died in coma. In this case, the relative hypocholesterinemia was of correct prognostic importance, while the measures of the nonnitrogenous constituents were not.

Case 7.—Male; aged 55; no jaundice; no fever; blood pressure, 170; moderate arteriosclerosis; Wassermann, negative; urine contained heavy trace of albumin, with hyaline and granular casts; general anasarca. Patient was restless, noisy and drowsy and a uremic state was certainly impending. Blood examination showed: nonprotein nitrogen, 144; urea nitrogen, 85; creatinin, 6; uric acid, 10; sugar, 0.152 per cent. and cholesterol, 1.85 mg. These figures bear out the severity of the condition. This patient grew steadily worse; delirium set in, and in two days he died in coma.

Case 8.—Male; aged 67. This patient was uremic and in very poor condition. The urine contained albumin, but no casts, and no acetone bodies. The blood pressure was 185. A pulmonary congestion was responsible for a fever

of 101.5 F. and a leukocyte count of 16,500. The figures for the blood were as follows: nonprotein nitrogen, 250; urea nitrogen, 150; uric acid, 10; creatinin, 18.7; sugar, 0.2 per cent. and carbon dioxid combining power 15; cholesterol, 0.65 mg. At the end of twenty-four hours, muscular twitchings developed, the patient became stuporous, went into coma, and died. Figures before death (and without fever) were as follows: nonprotein nitrogen, 250; urea nitrogen, 166; uric acid, 10; creatinin, 18; sugar, 0.24 per cent.; carbon dioxid combining power 44, and cholesterol 0.97 mg. These figures are typical of a uremic coma. At no time did this patient eliminate any phenolsulphonephthalein.

Case 9.—Male; aged 50; no fever; no jaundice; no arteriosclerosis; blood pressure, 200; Wassermann, negative; urine showed a large amount of albumin and hyaline and granular casts; dyspnea and general evidences of impending uremia, although the general condition of the patient was fairly good. Reasonably high figures for the waste products were found in examining the blood: nonprotein nitrogen, 55; urea nitrogen, 25; creatinin, 3.5; uric acid, 5; sugar, 0.2 per cent.; phenolsulphonephthalein elimination 38 per cent. The high figure for the uric acid is certainly suspicious. A decided relative hypocholesterinemia, 1.45 mg. was found. Ten days later, the patient became drowsy and stuporous and irrational and had to be tied in bed. Blood figures at this time, except for the cholesterol, again failed to show the gravity of the situation: urea nitrogen, 19; uric acid, 3.6; creatinin, 1.9; sugar, 0.10 per cent., while the cholesterol amounted to 1 mg., a very low figure under the circumstances. Two days later the patient went into coma and died.

Case 10.—Male; aged 27. This was a case of nephritis, based on syphilis, and despite the condition of the kidneys, was given vigorous antisyphilitic treatment. This patient did very well while under observation, and at no time showed any uremic tendencies. This case is reported to show the blood figures that are to be expected. There was no jaundice; no fever; slight general edema; the urine contained albumin and hyaline and granular casts; no headache; no vomiting; eyegrounds normal. Chemical examinations resulted as follows: Phenolsulphonephthalein elimination, 55; urea nitrogen, 15; creatinin, 1.5; sugar, 0.062 per cent., and cholesterol, 4.17 mg. Several months later the patient was under treatment in the dispensary, and was doing well. The cholesterinemia amounted to 3.49 mg. at that time. This patient was eventually lost sight of; however, continued observation should include a periodic examination of the blood cholesterol, and if it should be found to be steadily decreasing, the prognosis would be correspondingly worse. This fact is demonstrated by the following cases.

Case 11.—Male, aged 35; no fever; no jaundice; no arteriosclerosis; blood pressure, 240; urine contained albumin and hyaline and granular casts; intense headache, suggesting brain tumor; nausea; vomiting and diminished vision (fundi showed albuminuric retinitis); no edema; no rigidity of the neck; phenolsulphonephthalein elimination, 40; urea nitrogen, 19; uric acid, 2.6; creatinin, 1.5; carbon dioxid combining power, 55; cholesterol, 3 mg.

Two weeks later, with little change in his general condition (with roentgen-ray examinations of skull and spinal puncture negative) and the blood picture remaining the same, the cholesterinemia was found to have fallen to 2.42 mg. At the end of another two weeks, the cholesterinemia had dropped to 1.80 mg. The general condition of the patient became steadily worse; another two weeks found him stuporous and drowsy and passing only from 300 to 500 c.c. of urine a day. At this time, with the temperature subnormal (95 F.) and the picture of the urine unchanged, the cholesterinemia was found to be 1.10 mg. The following day, muscular twitchings set in, coma supervened and the patient died.

Necropsy revealed kidneys of a typical chronic interstitial nephritis. This case shows very well that it is the fall in the cholesterinemia that is of such prognostic importance.

The final case to be presented is one of exceedingly great interest. It is a case in which repeated examinations of the blood had been made, a case that had been carefully studied. The blood figures show well how the measure of cholesterinemia can be used in determining accurately the prognosis.

CASE 12.—Male, aged 23; no fever; no jaundice; considerable edema; blood pressure, 194; eyegrounds, normal; urine shows many hyaline and granular casts, and a heavy trace of albumin; Wassermann, negative; no evidence of impending uremia. The blood, which was turbid and chylous, showed 7.97 mg. of cholesterol, the highest figure I have ever obtained in a case of nephritis. At the same time, the blood showed nonprotein nitrogen, 77.0 mg.; urea nitrogen, 24; uric acid, 2.3; creatinin, 5.3; sugar, 0.124 per cent. Two weeks later, with conditions practically the same, except for some languor, the following figures were found: Cholesterol, 5.02 mg.; nonprotein nitrogen, 106; urea nitrogen, 55; uric acid, 7; creatinin, 13.6; sugar, 0.172 per cent.; carbon dioxid combining power, 18 volumes per hundred c.c.; blood indican, + +, and only a trace of phenolsulphonephthalein elimination. These figures distinctly show that retention of waste products is occurring.

Four days later, the patient had three convulsions and was stuporous, the blood figures were as follows: Cholesterol, 6.40 mg.; nonprotein nitrogen, 111; urea nitrogen, 67; uric acid, 7; creatinin, 14.1; sugar, 0.144 per cent.; carbon dioxid combining power 14 volumes; indican, + + + +. The following day, the patient's general condition was much improved (note the last rise in the cholesterinemia) and remained so for about ten days, but during the interval the following figures were obtained: Cholesterol, 4.97 mg. (a considerable fall); nonprotein nitrogen, 112; urea nitrogen, 63; uric acid, 5.5; creatinin, 11.1; sugar, 0.18 per cent.; indican, + + + +, and no elimination of phenolsulphonephthalein.

At this stage of his illness, the patient again became worse, convulsions of increasing severity and duration, with dulness and apathy set in, and the following figures were obtained: Cholesterol, 3.39 mg.; nonprotein nitrogen, 125; urea nitrogen, 59; uric acid, 12.5; creatinin, 11.6; sugar, 0.120 per cent.; carbon dioxid combining power, 24 volumes; indican, + + + +. Five days later, with convulsions, stupor and restlessness continuing, the following figures were obtained: Cholesterol, 3.38 mg.; nonprotein nitrogen, 117; urea nitrogen, 72; uric acid, 4.2; creatinin, 12.3; sugar, 0.153 per cent.; carbon dioxid combining power, 29.6 volumes (treatment directed to combat the acidosis); indican, + + + +. The following day convulsions became very frequent, stupor deepened into coma, and the patient died. Blood obtained before death gave the following figures: Cholesterol, 2.49 mg.; nonprotein nitrogen, 144; urea nitrogen, 100; uric acid, 12.5; creatinin, 13.4; sugar, 0.20 per cent.; carbon dioxid combining power, 24 volumes; indican, + + + +.

Here, then, is a case in which the cholesterinemia fell gradually from 7.97 to 2.49 mg. in the course of six weeks, while the nonprotein nitrogen constituents of the blood steadily increased in amount. It is the fall in the measure of cholesterinemia that is the significant feature in estimating the prognosis in any given case.

It has long been my belief that the lipoids of the blood play a rôle analogous to an antitoxin, and are intimately associated in immunologic processes. The lipoids seem to act as a protection to the animal organism, and are known to counteract certain poisonous substances. Recent literature abounds in substantiation of this belief.

PROGNOSTIC VALUE OF CHOLESTERINEMIA IN CHRONIC NEPHRITIS

Case	Sex	Age	Blood Pressure	Urine Analysis			Blood Analysis, Mg. per 100 C.c.								Remarks
				Phenolphthalein	Albumin	Microscopical	Cholesterol, Gm. per 1,000	Non-protein Nitrogen	Urea N.	Creatinin	Uric Acid	Sugar, per Cent.	Indican	CO_2 Vols. 100	
1	M	66	220	..	+	H. and G. casts	2.05	...	55	1.0	2.7	0.132	...	....	General condition not good
2	F	60	...	..	+	H. and G. casts	1.73	...	...	....	....	....	...	....	Patient died in coma in three days
3	F	59	...	..	+	H. and G. casts	1.65	125	100	13.4	5.5	0.129	...	10.0	Vomiting, stupor, coma, death
4	M	50	180	79	+	H. and G. casts	2.34	...	17.5	1.5	1.4	0.09	...	....	General condition good
			170	..	+	H. and G. casts	1.43	110	58	3.5	5.0	0.136	...	42.0	Threatened uremia
					+	H. and G. casts	2.02	41	16	1.1	1.0	0.146	...	48.5	Early death in coma
5	F	61	210	..	+	None	2.93	...	16	1.5	2.7	0.106	...	....	Death from cerebral hemorrhage
6	M	52	150	..	+	H. and G. casts	1.77	...	35	1.3	....	0.112	...	31.0	Coma, uremic
					+	H. and G. casts	....	...	31	2.5	2.3	0.12	...	48.0	Coma, death
7	M	55	170	0	+	H. and G. casts	1.85	144	85	6.0	10.0	0.152	...	....	Uremic coma and death
8	M	67	185	0	+	None	0.65	250	150	18.7	10.0	0.2	...	15.0	Uremic
				0	+	None	0.97	250	166	18.0	10.0	0.24	...	44.0	Coma, death
9	M	50	200	38	+	H. and G. casts	1.45	55	25	3.5	5.0	0.2	...	....	No pending uremia
					+	H. and G. casts	1.09	...	19	1.9	3.6	0.1	...	....	Coma, death
10	M	27	...	55	++	H. and G. casts	4.17	...	15	1.5	....	0.06	...	....	General condition good
					++	H. and G. casts	3.49	...	...	....	....	....	...	....	General condition good
11	M	35	240	40	+	H. and G. casts	3.00	...	19	1.5	2.6	....	...	55.0	Nausea, vomiting
					+	H. and G. casts	2.42	...	....	....	....	....	...	....	No change
					+	H. and G. casts	1.80	...	...	....	....	....	...	....	Stupor, drowsy
					+	H. and G. casts	1.10	...	...	....	....	....	...	....	Muscular twitchings, coma, death
				tr	++	H. and G. casts	7.97	77	24	5.3	2.3	0.124	...	....	No evidence of impending uremia
12	M	23	194	tr	++	H. and G. casts	5.02	106	55	13.6	7.0	0.172	2+	18.0	Some languor
					++	H. and G. casts	6.40	111	67	14.1	7.0	0.144	4+	14.0	Three convulsions
				0	++	H. and G. casts	4.97	112	63	11.1	5.5	0.18	4+	....	Occasional convulsions
				0	++	H. and G. casts	4.18	100	67	12.8	8.3	0.135	...	....	Convulsions, apathy
			170	..	++	H. and G. casts	3.39	125	59	11.6	12.5	0.12	4+	24.0	Drowsy, dulness, convulsions
					++	H. and G. casts	3.38	117	72	12.5	4.2	0.113	4+	29.6	Stupor, convulsions
					++	H. and G. casts	2.49	144	100	13.4	12.5	0.20	4+	24.0	Convulsions, coma, death

"Cholesterol is no fortuitous component of the organism." [2] Barbary [3] believes that cholesterol stimulates the production of antibodies. In his hospital at Nice, where during twenty months he cared for 767 wounded and 797 sick soldiers, he had a strikingly low mortality: four deaths among the wounded and nine deaths among the sick. He attributes the good results obtained to the general use of the following mixture: Cholesterin, 0.2 gm.; camphor, 0.5 gm.; strychnin sulphate, 0.0005 gm.; in 5.0 c.c. of olive oil washed in alcohol.

Urra [4] found that cholesterol neutralizes toxins. He found that a hypercholesterinemia is to be found in all severe toxic processes at the time the toxemia is being overcome, referring especially to nephritis and typhoid fever. Several years ago [5] I showed that a definite hypocholesterinemia exists during the fever period of typhoid, a slow return to normal as the fever approaches normal, and a decided hypercholesterinemia during convalescence.

Manfredi [6] has shown that the addition of cholesterol to cultures of typhoid bacilli (even in amounts less than are found in the blood stream) checked the growth of the organism. Other organisms, such as the colon bacillus, the streptococcus of erysipelas and puerperal fever, the staphylococcus, diphtheria and cholera bacilli, were also checked in their growth. The hypercholesterinemia of pregnancy is acknowledged to be a fact, and as the result of the study of more than one thousand cases, I believe a relative hypercholesterinemia is to be found in puerperal fever.

Goormaghtigh [7] has shown that the suprarenal supplies cholesterol to the blood stream in infectious diseases, and in grave infections, terminating fatally, the reserve of cholesterol was demonstrated to be exhausted.

Morato and Villanueva [8] have shown that the injection of cholesterol with typhoid vaccine hastened the production of antibodies and agglutinins. They cite researches of others who have shown the benefit following the administration of cholesterol in those conditions in which a hypocholesterinemia is found.

Cholesterol has been shown to be antitoxic to the venom of a viper and a cobra. It has been shown to neutralize the toxin of sausage

2. Editorial, J. A. M. A. **62**:620 (Feb. 21) 1914.

3. Barbary: Cholesterin and Camphor to Mobilize and Reinforce the Natural Defensive Powers, Bull. de l'Acad. de méd., Par. **76**:221.

4. Urra: The Defensive Lipoids, Semana méd. **24**:506.

5. Hennes: Cholesterinemia, Proc. New York Pathol. Soc. **13**: No. 7.

6. Manfredi: Effect of Cholesterol in Culture Medium on Development of Germs, Riforma méd., Naples **33**:849.

7. Goormaghtigh: The Functioning of the Suprarenal Capsules in Infections, Arch. méd., Belges **70**:697.

8. Morato and Villanueva: Cholesterol a Factor in Immunity and in the Production of Agglutinins, Med. Ibera, Madrid **9**: No. 107.

poisoning and to attenuate tuberculin, and it has been used in the treatment of tuberculosis and various anemias.

These references to the literature have been presented in justification of my belief that cholesterol plays some protective rôle in the animal organism. The prognostic value of the measure of cholesterinemia in chronic nephritis becomes of greater interest and importance because of these facts. The researches of the past years seem to justify a conclusion I came to eight years ago: "Cholesterinemia seems to be of prognostic importance in some diseases and an indicator of their severity. Researches in cholesterinemia are still in their infancy. Much work is necessary before the many problems this lipoid presents in its relation to the organism, both under normal and pathologic conditions, can be solved. We have yet to determine more exactly, above all, its origin and destiny, the physiology and pathology of the quantitative variations in the blood, the significance of these variations and the possible rôle cholesterin can play in therapy."[5] Many of these problems have since been solved.

I wish to acknowledge my indebtedness to Mr. A. Bernhard, in charge of the chemical laboratory of the Lenox Hill Hospital, for the chemical examinations of the blood in the cases reported.

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CLINICAL OBSERVATIONS ON UNUSUAL MECHANISMS OF THE AURICULAR PACEMAKER

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In the clinical records from the electrocardiographic laboratory of the Massachusetts General Hospital are some examples of unusual mechanisms of the auricular pacemaker worthy of discussion.

1. AN UNUSUAL TYPE OF AURICULAR PAROXYSMAL TACHYCARDIA

Simple paroxysmal tachycardia is defined as a tachycardia of sudden onset and sudden offset, with a striking regularity of rate, and arising from an abnormal point or ectopic focus in the auricles or ventricles. Such, indeed, is the usual occurrence. Some irritable spot in the heart takes away the initiative or impulse formation from the pacemaker or sino-auricular node in the right auricle. Whipping up the heart on its own account, it carries on this dominant rhythm till exhausted when once more the normal pacemaker resumes its work after a short pause.

Theoretically, an abnormal pacemaker like the ectopic focus is beyond nervous control and ceases its activity spontaneously. Sometimes, one finds clinically, however, that nervous influences may readily induce a paroxysmal tachycardia, and other nerve stimuli, such as pressure on the vagus nerve or eyeball, may stop it. The mechanism is not easy to explain in a number of such cases, but the important exciting factor is certainly extracardiac.

In paroxysmal tachycardia the electrocardiogram usually confirms the idea that the new pacemaker is "ectopic" by presenting a very abnormally shaped P or auricular wave. Normally, the P wave is upright in the electrocardiogram, but in paroxysmal tachycardia of the usual auricular type, the P wave is apt to be inverted.

Rarely one finds a case of auricular paroxysmal tachycardia in which the ordinary definition fails to hold. Such an instance is shown in Figures 1 and 2. Short paroxysms of tachycardia occur in which there is a markedly rapid, but not immediate, increase in the heart rate to the maximum, and a tendency to offset of the same type. Moreover, the shape of the P wave is normal or close to normal. The explanation of such a paroxysm of tachycardia is that it results from unusual nervous stimulation of the normal pacemaker or of a point in close proximity to the normal pacemaker in the sino-auricular node.

The measurements of the intervals between the heart beats in the case described here normally were about 0.77 second. The measure-

ments between the heart beats at the beginning of the paroxysm in Figure 2 are as follows: 0.651 second (the beat preceding the paroxysm), 0.407, 0.425, 0.384, 0.323, 0.316, 0.325, 0.308, 0.327, 0.317, 0.336, 0.316. The measurements of the intervals at the end of the paroxysm in Figure 2 were: 0.323, 0.318, 0.310, 0.370, 0.830 (the beat after the paroxysm). At the height of the paroxysm, also shown in Figure 2, the intervals were: 0.316 second, 0.323, 0.310, 0.326. The normal rate of the heart was 78 per minute. The rate of the tachycardia at its maximum was about 188 per minute.

CASE 1.—R. M., male, aged 21 years, was born in Italy. He was a worker in a jewelry shop.

Family History.—One sister was demented.

Past History.—The patient has had no serious illness in the past. He never has had rheumatic fever, chorea or tonsillitis. He always has been nervous.

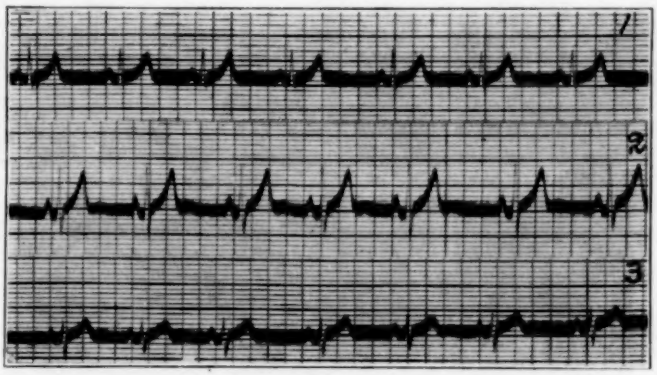

Fig. 1.—Electrocardiogram of R. M. (Case 1), showing normal rhythm in all three leads. T wave in Lead 2 is very high. Some respiratory arrhythmia is present. Lead 1 above, Lead 2 in middle and Lead 3 below. Abscissa = 0.2 sec.; ordinate = 10^{-4} volt.

Present Illness.—His present trouble, "palpitation," began seven years ago with a rapid heart beat in short paroxysms with choking sensation. He feels better now and then, and sometimes has no spells for months.

Examination.—This was entirely negative, except for frequent short paroxysms of tachycardia. The Wassermann reaction was negative. Roentgenogram of the heart was normal. Basal metabolism estimation was normal.

This patient has been under observation for five years, being first seen in October, 1914. He has constantly shown the same phenomenon, but has remained in good health otherwise; he has not had to stop work. Unfortunately, the paroxysms were too brief for experimentation, rarely lasting more than ten seconds each. While being examined

under particularly exciting conditions, paroxysms occurred frequently, his heart at times beating more paroxysmally than normally.

Somewhat comparable is the voluntary acceleration of the rate of the pacemaker as seen in published electrocardiograms.[1] In the voluntary acceleration cases, however, the increase in rate is less rapid. Carter and Wedd[2] have reported a case of paroxysmal tachycardia characterized by unusual control of the fast rhythm. The focus of the ectopic rhythm was apparently near the pacemaker and could be abolished at will, but the rate of the paroxysm was quite regular at about

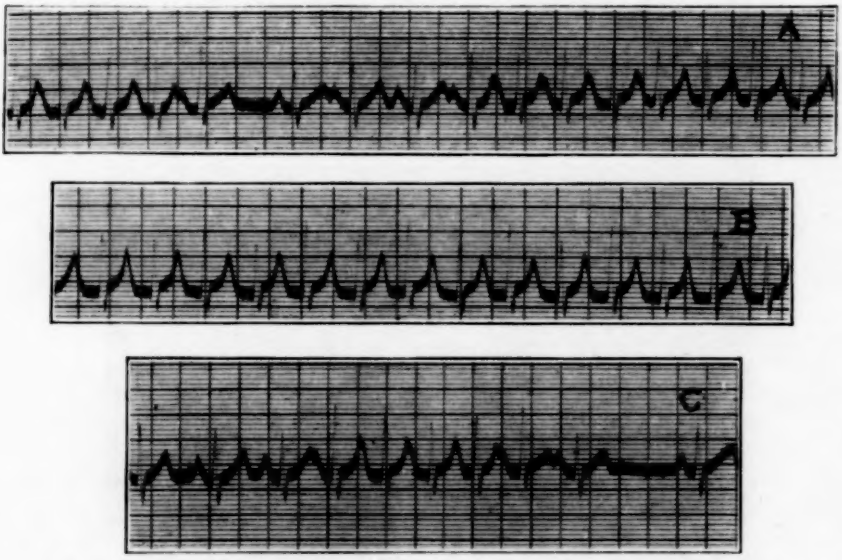

Fig. 2.—Electrocardiograms showing paroxysms of tachycardia of R. M. (Case 1). All are of Lead 2. In the upper record (A) the offset of one paroxysm and the onset of another are shown. In the middle record (B) a paroxysm appears at its height. In the lower record (C) a short complete paroxysm is photographed. Observe in this lower record particularly the gradual onset and gradual offset.

200 (196 to 204) and was not under accelerator control. In the abrupt transition from an abnormal rate to normal, this case differed from the one reported here.

Recently, Prof. Giovanni Galli,[3] of Rome, called attention to the nomotopic (nomos, custom; topos, place) type of paroxysmal tachy-

1. Favill, J., and White, P. D.: Heart **6**:175, 1917.
2. Carter, E. P., and Wedd, A. M.: Arch. Int. Med. **22**:571 (Nov.) 1918.
3. Galli, G.: Arch. d. mal. du coeur, **12**:289, 1919.

cardia. He writes on the manner of termination and onset of the attacks in nomotopic paroxysmal tachycardia, and gives the following points in favor of the possible diagnosis of sino-auricular paroxysmal tachycardia:

1. The sino-auricular node is composed of irritable muscle tissue Why should it not be the source, then, occasionally of paroxysmal tachycardia?

2. Vagal excitation may influence paroxysmal tachycardia.

3. Atropin may induce paroxysmal tachycardia (Galli mentions a case in which the heart rate jumped from 90 to 200 after administering atropin).

4. Emotion may start a paroxysm.

5. The Valsalva experiment may sometimes stop a paroxysm.

6. There was a progressive increase ("crescendo") and decrease ("diminuendo") in the paroxysm in some of the tracings he obtained. Thus, there was a "parabolic development" with termination by "lysis."

7. Sometimes, at the onset of a "normal sino-auricular tachycardia" there may be a brusque change in heart rate.

8. The P wave in the electrocardiogram may appear of normal or nearly normal shape.

9. Experimental stimulation of the extracardiac nerves, for example, the right stellate ganglia, may induce a marked tachycardia.

10. Nomotopic paroxysmal tachycardia seems to have a better prognosis than the usual paroxysmal tachycardia, as one might expect.

2. VARIATION IN POSITION OF THE PACEMAKER AS SHOWN BY THE SHAPE OF THE P WAVE, THE LENGTH OF THE P-R INTERVAL AND THE HEART RATE

Lewis, Meakins and White [4] showed experimentally that the pacemaker in the sino-auricular node of a dog's heart varies its position with vagal stimulation, moving to or near the distal or tail end of the node. Its movement downward toward the ventricle tends to shorten the auriculoventricular interval or P-R interval as expressed electrocardiographically, but since ordinarily vagal stimulation depresses the auriculoventricular junctional tissues as well as the head of the sino-auricular node, the P-R interval may be actually lengthened rather than shortened.

Einthoven [5] observed the change in the shape of the P wave with prolongation of the P-R interval in vagal stimulation. Goddard [6] noted that the size and shape of the P wave may vary at different times in the same curve, and an inverted P in one record may appear upright in a later tracing, and vice versa.

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4. Phil. Tr. Roy. Soc. London **205**:375 (Series B) 1914.
5. Einthoven, W.: Arch. f. d. ges. Physiol. **122**:517 1908.
6. Goddard, C. H.: Arch. Int. Med. **16**:633 (Oct.) 1915.

Wilson [7] has discussed the mechanism of the pacemaker within the sinus node or within its immediate neighborhood, as well as its migration from the sinus to the *a-v* node, and has published electrocardiograms illustrating the migration resulting from respiratory influences.

According to theory, with the migration of the pacemaker from the head toward the tail of the sino-auricular node and to the *a-v* node, the P wave becomes flattened and finally inverted, the P-R interval becomes shorter, providing there is little or no simultaneous vagal effect on the *a-v* junctional tissue, and the heart rate drops.

Two electrocardiograms obtained at the Massachusetts General Hospital illustrate such a variation in position of the pacemaker by tendency to negativity of the P or auricular deflection and by a shortening of the P-R interval, and in one case by the decrease in the heart rate. The first instance, the type usually seen, was the result of vagal pressure in a man aged 33 years, who was seriously ill with chronic nephritis, and cardiac enlargement and weakness. The electrocardiogram, Lead 2, is shown in Figure 3. Here, right vagal pressure was applied at first in

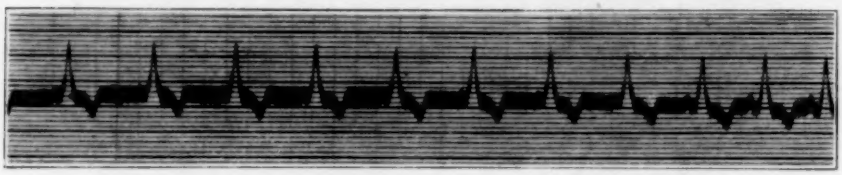

Fig. 3.—Electrocardiogram (Lead 2) of E. M. showing the effect of right vagal pressure on the auricular pacemaker. The dislocation of the pacemaker toward the ventricle is indicated by the change from normal in the shape of the P wave, the shorter P-R interval and the slower heart rate. The T wave is markedly inverted.

the record and then released. The P wave at first flattened, returns to a normal upright shape. The P-R interval at first measuring 0.099 and 0.098 second, becomes at the end of the record 0.146 and 0.144 second. The heart rate at first 83, becomes 108. Of interest in this case is the fact that the sino-auricular node has been definitely depressed by the vagal stimulation, but the *a-v* conduction has not been slowed.

The second record is that obtained spontaneously from an elderly lady (Mrs. M.) with arteriosclerosis and an arrhythmia consisting of ventricular premature contractions. In the course of one minute, P waves of different shapes were found. The electrocardiogram, Lead 2, is shown in Figure 4. Apparently the pacemaker is moving about rap-

7. Wilson, F. N.: Arch. Int. Med. **16**:86 (July) 1915; Am. J. Dis. Child. **10**:376 (Nov.) 1915.

idly in the node, in the first record alternating between a high and low position, the P-R intervals alternating as well as the change in shape. The first low P carries with it an interval of 0.124 second; the next P, a much higher one, a P-R interval of 0.152 second. The following P-R intervals continue to alternate: 0.124, 0.155, 0.125, 0.155 second. The interauricular intervals are 0.989, 0.977, 0.988, 0.995 and 1.018 seconds. Finally, the inverted P waves in the second record (Fig. 4) have very short P-R intervals of 0.099, 0.103, 0.101 second. It will be noticed that a premature ventricular beat interrupts the rhythm and is followed by a deeply inverted P wave (retrograde). It is probable that the inverted P wave arises from the region at the lower end of the *s-a* node, at the junction of the auricle with the *a-v* node, or between the two, as indicated by shape and by P-R interval. The interval between the

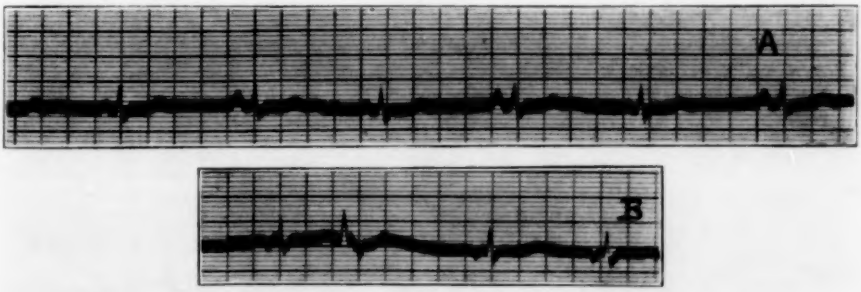

Fig. 4.—Electrocardiograms (Lead 2) of Mrs. M. (Case 3), indicating in the upper record (A) alternation in the position of the pacemaker as shown by the alternating change in shape of the P wave and by the alternating length of the P-R interval. In the lower record (B) the auricular impulse is arising from a point still nearer the ventricle as shown by the inversion of the P wave and by the short P-R interval. A ventricular premature beat with retrograde impulse to the auricles interrupts the rhythm in the lower record (B).

two rhythmic inverted auricular waves in this strip is 0.866 second, which is less than that between the more normal auricular complexes in the upper record. The explanation of this is not clear, unless, perhaps, the premature contraction is disturbing the rhythm.

These records were made from a private patient during the war by Miss Mabel Hopkins, and there was no opportunity to investigate the condition further. The patient had not had digitalis. Of particular interest in this case is the alternation in the site of the pacemaker.

3. SUDDEN HALVING OF THE AURICULAR RATE ("SINO-AURICULAR HEART-BLOCK") AFTER EXERCISE

CASE 2.—W., a young man, aged 24 years, a renowned athlete in college football two years before, showed a sudden halving of the pulse rate coming

on one minute after a fast run of about one-quarter of a mile. Electrocardiograms of this occurrence showed the onset of the so-called sino-auricular heart block, the sino-auricular pacemaker changing abruptly from a rate of 88.2 per minute to one of 44.8 per minute, rising shortly to 53.6 (Fig. 5). The rate remains slow. The man was healthy.

The sino auricular block in this athlete was undoubtedly due to marked vagal action following exercise. It is possible that this phenomenon occurs occasionally in athletes.

The more usual form of sino-auricular block, generally a digitalis effect due to the depression of the sino-auricular pacemaker, is shown in Figure 6. This is an electrocardiogram of a woman, aged 33 years, with heart apparently normal, but with a cough of obscure origin. She was seen in the outpatient department of the Massachusetts General Hospital during the war. She had not had digitalis.

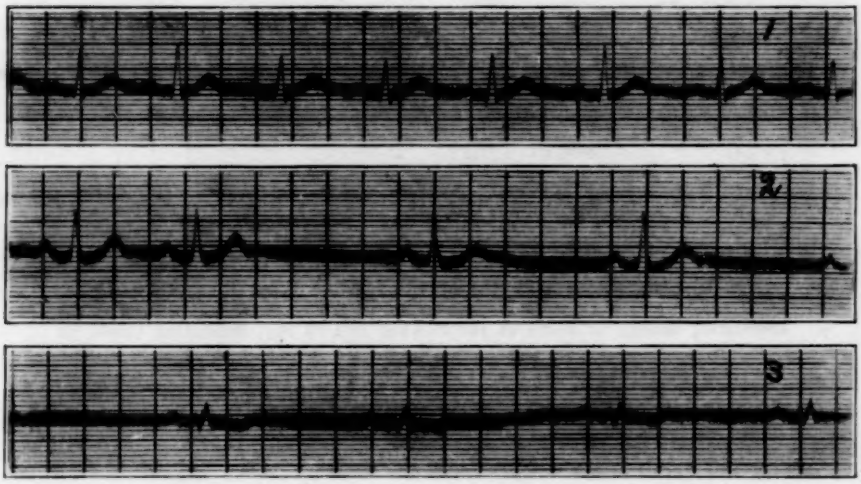

Fig. 5.—Electrocardiograms showing Leads 1, 2 and 3 of P. D. W. taken in order immediately after exercise. In the middle record occurs the sudden halving of the auricular rate (sino-auricular heart block) from 88.2 to 44.8 per minute.

Levine,[8] in 1916, reported four cases of sino-auricular block seen at the Peter Bent Brigham Hospital. Three of these patients had had digitalis. He collected fourteen cases from the literature, four of which are very doubtful, because in two no graphic records were made, and in the two others only radial tracings were taken. The arrhythmia due

8. Levine, S. A.: Arch. Int. Med. **17**:153 (Jan.) 1916.

to sino-auricular block was apparently the result of digitalis in seven cases, but in five others there was no statement as to whether or not digitalis had been given.

White,[9] in 1916, reported three cases seen at the Massachusetts General Hospital, in which all evidence of auricular action was temporarily abolished by digitalis, that is, auricular standstill or complete sino-auricular block was present. In another case, reported by White,[10] there was evidence of sinus bradycardia due to digitalis, in which instance the auricular rate was 41 and the ventricular rate 82 at times.

Thomas Lewis, in his "Clinical Electrocardiography," published two electrocardiograms of sino-auricular block, one from a case of mitral stenosis and one from a case of exophthalmic goiter. In 1913 [11] he reported a case of unusual bradycardia in which there was no trace of auricular activity in the electrocardiogram or jugular tracing. No statement as to digitalis administration was made in this case.

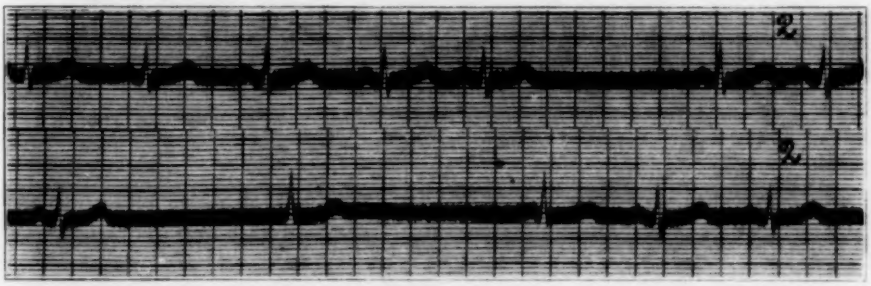

Fig. 6.—Electrocardiogram (Lead 2) of E. L. showing sino-auricular heart block, not resulting from the action of digitalis.

Brown [12] recently described a case of sino-atrial heart block in a child, 11 years of age, with acute arthritis. Here there had been no digitalis administration. Atropin abolished the block.

In spite of the rarity of its publication, it is probable that sino-auricular block occurs more frequently than we have been led to suspect.[13]

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9. White, P. D.: Boston M. & S. J. **175**:233 (Aug. 17) 1916.
10. White, P. D.: Arch. Int. Med. **18**:244 (Aug.) 1916.
11. Lewis, T.: Quart. J. Med. **6**:221, 1913.
12. Brown, N. W.: Arch. Int. Med. **24**:458 (Oct.) 1919.
13. Another case of sino-auricular block has been seen at the Massachusetts General Hospital since this article was written. This makes the seventh seen at this hospital during five years, three with complete and four with partial sino-auricular block. The patient was a woman, aged 56 years, with cardiosclerosis with slight cardiac failure; she had not had digitalis.

SUMMARY

Three clinical examples of unusual mechanism of the auricular pacemaker are reported:

1. Paroxysmal tachycardia arising in or very near the sino-auricular node and not showing an absolutely abrupt onset or offset.

2. Migration of the pacemaker in the sino-auricular node, two foci alternating action in one case.

3. Sudden halving of the auricular rate (sino-auricular block) after exercise.

FETID SPIRILLAR BRONCHITIS AND PULMONARY GANGRENE

P. NOLF, M.D.
LIÉGE, BELGIUM

Castellani [1] noted in soldiers of the Italian Army the not infrequent occurrence of an affection of the respiratory tract which he had described previously at Ceylon, and of which he had recognized the specific agent. This affection he had termed *bronchospirochetosis.* It appears under two aspects: A form of short duration, lasting from one to three weeks, and running its course after the fashion of an acute bronchitis, with fairly high temperature during the early days; a form with a prolonged course simulating a chronic bronchopneumonia of long duration, several years in most cases, but sometimes taking on a malignant character, with irregular fever, hemoptysis, progressive enfeeblement and emaciation, and lethal termination.

The specific parasite is a spirillum, *Spirochaeta bronchialis,* very polymorphous, from 4 to 30 microns long, 0.2 to 0.6 micron in thickness, presenting from two to eight undulations and sometimes more, the extremities of variable shape, often pointed and without flagella.

H. Violle [2] published an article on an affection of the respiratory tract characterized by bloody expectoration, which he termed hemorrhagic bronchitis. The secretion of the bronchial mucosa is abundant, nearly a quarter of a liter in twenty-four hours. It is tenacious, stringy, viscous, homogeneous, of a bright rosy color, resembling gooseberry juice. It is sufficient, says Violle, to have seen it once to escape the danger of confounding it with tuberculous hemoptysis. On examination of the chest, the results vary: sometimes nothing, sometimes a slight enfeeblement of the vesicular murmur, sometimes signs of a simple bronchitis with or without areas of pulmonary congestion; sometimes, finally, very clear cut signs of chronic bronchitis and emphysema. The general condition is good, often, indeed, very good; there is no fever; the expectoration contains spirochaetes in great abundance. The organisms show an extraordinary polymorphism, and this variation in their shape and dimensions is one of their special characteristics.

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1. Castellani, A.: Note sur la "Broncho-spirochaetose" et les bronchites mycosiques, affections simulant quelquefois la tuberculose pulmonaire. Presse méd. **25**:377, 1917.

2. Violle, H.: La spirochaetose bronchopulmonaire (bronchite sanglante). Rev. gén. de clin. et de thérap. **32**:144, 1918.

This affection, for which the author suggests the name of *hemorrhagic bronchitis with spirochetes,* justifies, generally a favorable prognosis. After ten or fifteen days the expectoration ceases to be mucohemorrhagic, and complete recovery follows fairly rapidly. Nevertheless, relapses, as in the acute form described by Castellani, are surprisingly frequent, and the disease may take on a chronic course with varying periods of exacerbation.

During the war I described, in collaboration with Dr. P. Spehl,[3] an acute affection of the respiratory tract, the clinical aspect of which is that of a bronchitis or a bronchopneumonia with the special characteristic that the breath of the patient and his expectoration becomes fetid rather early in the course of the development of the disease; the etiologic agent appears to be a spirillum. This malady, so far as we know, has not been observed elsewhere. It would seem to us to be distinguished from the bronchospirochetosis of Castellani and from the bronchitis due to the spirillum described in France by H. Violle.

In my opinion the disease observed by us is not of tropical origin. It is probable that it must be met with in times of peace among the civil population of countries of temperate climate. It has seemed to me that it might be interesting to bring our observations to the attention of the English speaking medical public.

Case 1.—Dec. . . . A., aged 25, infantryman, fell ill, April 23, 1917, and experienced suddenly, a sensation of general malaise, with headache, pains in the extremities and loins. Cough soon followed, with frothy, whitish expectoration, and a few days later laryngitis. On entry into the hospital, April 29, the patient complained of headache and of general pains. Temperature from 38.6 to 39.4 C.; pulse accelerated, from 104 to 112; respiration, quiet; cough, paroxysmal, fatiguing and accompanied by mucopurulent expectoration, whitish gray, of a very fetid odor. There was laryngitis; the voice was hoarse; the naso-pharynx was intact. On examination of the thorax the resonance was normal. Auscultation showed a few sibilant râles, especially at the right base. The general condition was satisfactory.

In the succeeding days the bronchitis increased, the cough became more frequent as well as the expectoration, the fetor of which increased. May 4, the percussion note was diminished at the right base, and auscultation revealed, chiefly at this point, numerous subcrepitant râles. The temperature fell below 37 C., May 9 (seventeenth day) and did not rise again until May 20 (twenty-eighth day) when, without apparent cause, there was a slight congestive attack at the right base; at the end of two days the temperature fell again to normal. The local trouble was slow in improving. The râles diminished after May 11 but did not disappear until the middle of June. Laryngitis persisted until the end of the same month.

After May 5, microscopic examination of the sputum revealed for about three weeks the presence of numerous spirilla. Their number together with the fetor of the expectoration diminished after May 20. They disappeared May 25, but the breath of the patient remained fetid until May 29.

3. Nolf, P., and Spehl, P.: La bronchite fétide à spirilles, Arch. méd Belges **71**:1, 1918.

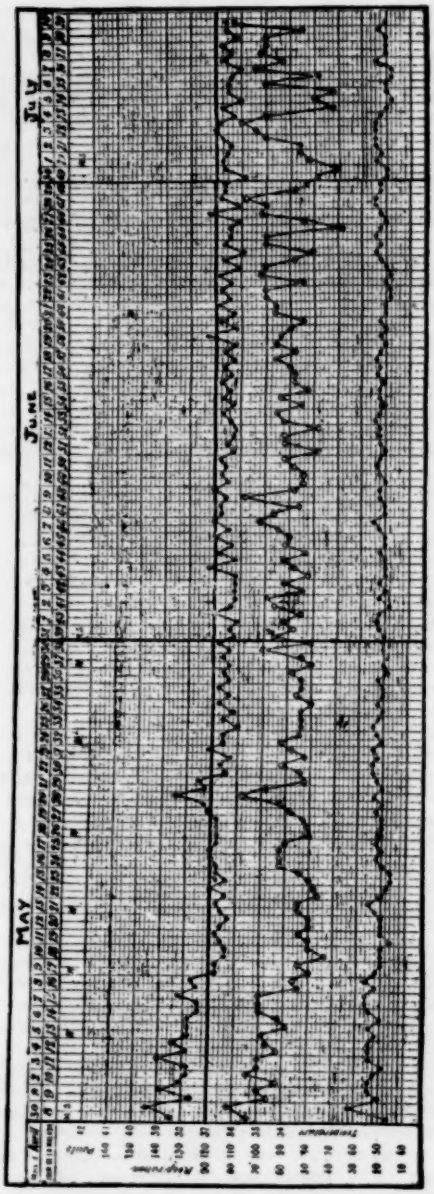

Figure 1

Treatment consisted of warm, moist packs for the chest, with application of tincture of iodin in enemas of creosote and in intravenous injections of novarsan, repeated from May 5 to the end of the month, every five days, in a dose of 45 cg. The amelioration of the general condition became apparent after the first injecton and much more so after the second. The local lesions were not influenced so rapidly. Later, heliotherapy appeared to accelerate convalescence.

For the laryngitis insufflations of sodium benzoate were relatively inefficacious.

Case 2.—Theun., aged 27, infantryman, suffering from a simple cold, complained on June 29, 1917, of general malaise, thoracic pain, headache and a little difficulty in swallowing. He coughed, expectorated moderately and showed a little fever.

Entering the hospital July 6, on the first clinical examination there was noted a rather elevated temperature (from 38 to 39.5 C.), a pulse of 100 and slight increase in the size of the spleen which reached the costal border on deep inspiration.

The arterial pressure was normal (155/80, Pachon). Examination of the thorax was negative. Chemical examination of the urine, including Diazo reaction and cultures, blood culture, Widal reaction, search for malarial parasites, were negative. There was a slight leukopenia (from 4,400 to 4,800 leukocytes); the blood formula (lymphocytes 19, mononuclears, medium 5, large 1, intermediate 1, polymorphonuclear neutrophils 13, eosinophils 1) was normal.

Up to July 17 (nineteenth day) the fever oscillated continually between 38 and 39.5 C. The patient raised, without particular auscultatory signs, a moderate fetid bronchial expectoration which did not contain tubercle bacilli but spirilla in considerable numbers. From this time on a series of injections of novarsan (from 30 to 60 cg.) was begun, at intervals of four days, and as adjuvant medication, there was prescribed a daily enema of creosote. After six injections, representing only about 1.95 gm. of novarsan, the spirilla disappeared from the expectoration.

However, this treatment remained without action on the general condition of the patient, which became aggravated, or on the temperature, which continued to oscillate between 38.5 and 39.8 C.

August 20 (fifty-second day) a laryngitis appeared. The fetid expectoration increased, medium moist râles appeared at both bases. The pulse increased to 125, the respiration to 30. Intravenous injections of peptone, digitalin and strychnin were added to the previous medication. Despite all, the condition of the patient became worse, and death followed September 9 (seventy-third day).

At the necropsy there was edema of both lungs, but no tubercles. At the hilum of the right lung were four enlarged glands. In the pulmonary tissue were some miliary abscesses which do not contain spirilla, tubercle bacilli or giant cells. The spleen was enlarged. The heart, liver, kidneys, intestines were normal.

Case 3.—Dav. J., aged 26, detached for service at a hospital, fell ill suddenly August 20. On this date he showed a general malaise, depression, chills, pain in the chest, dyspnea, cough and expectoration.

On entrance (August 23) the patient was much prostrated; the body was covered with cold sweat; the face and extremities were cyanotic. The temperature was 39.5 C.; the pulse and respiration were accelerated; the cough was frequent, expectoration was scanty, mucopurulent, colorless, odorless and aerated. The tongue was moist and white; there was complete anorexia. The urine was deeply colored and showed traces of glucose and albumin.

The upper respiratory tract was normal; percussion of the lungs showed nothing suspicious. On auscultation, disseminated sibilant râles could be heard. Hot packs were applied to the chest and this was painted with tincture of iodin. During the following days, the fever remained elevated; pros-

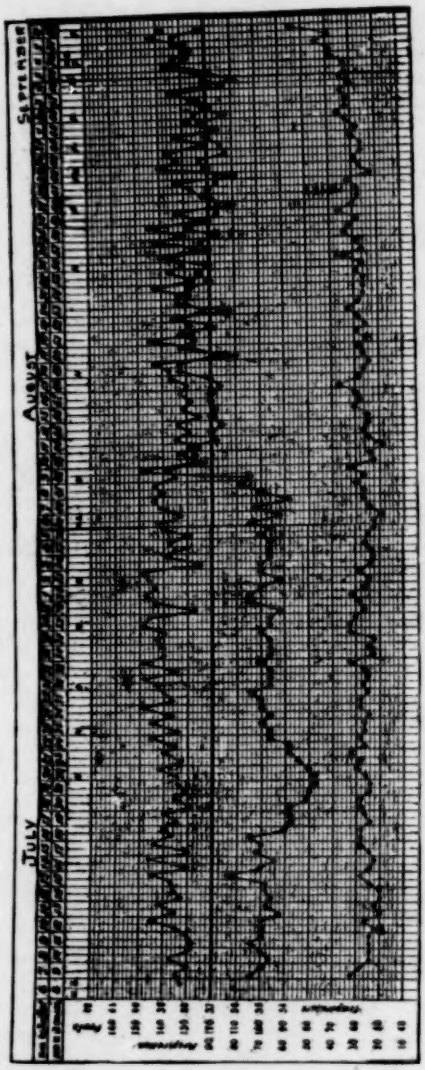

Figure 2

tration and dyspnea persisted; the sibilant râles diminished greatly, but the expectoration increased, became greenish in color and of a foul odor. Microscopic examination made August 26 revealed spirilla in moderate numbers, but no tubercle bacilli. A series of intravenous injections of novarsan was begun (60 cg. on August 26 and 29 and on September 5 and 12) and peptone was given intravenously as an adjuvant (1 gm. on August 31 and September 2, 4, 6, 8, 10, 12 and 17).

The spirilla disappeared after September 3, but the expectoration remained fetid up to the middle of the month. Gradually, the pulmonary symptoms receded, the general condition improved, and recovery was complete at the beginning of October.

Case 4.—Picr . . . M., aged 24, infantryman, was taken ill Jan. 13, 1918, with general fatigue, left pleurodynia, severe chill, fever and abundant sweating. This was followed by cough and rusty expectoration. He entered the hospital, January 16, with symptoms of congestion at the base of the left lung. The temperature was 39.5 C.; the pulse and respiration were accelerated. Moist warm packs for the chest were prescribed.

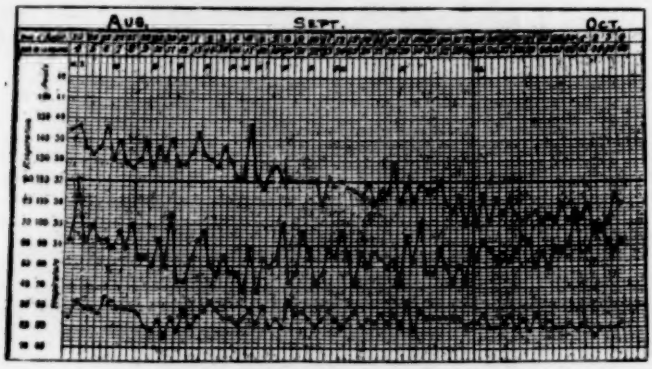

Figure 3

Two days afterward, moist râles were heard at both bases; in the right scapular region there were crepitant râles and slight dulness.

The breath became fetid. The expectoration was mucopurulent and of a greenish color. A daily enema of creosote, 2 gm. to 100 c.c., and an intravenous injection of 30 cg. of novarsan were prescribed. Examination of the blood revealed 15,500 leukocytes per c.mm., and a leukocyte formula of 9 lymphocytes, 5 medium sized mononuclears, 5 large, 2 intermediate forms, and 79 polymorphonuclear neutrophils. The sputum showed occasional spirilla in addition to an abundant and varied bacterial flora. Injections of novarsan (45 to 60 cg., repeated every five days) and intravenous injections of peptone were continued to March 18. The temperature fell irregularly to February 6, rising several days afterward and remaining between 37 and 38 C. The auscultatory signs (moist râles, fugitive areas of blowing breathing corresponding to areas of bronchopneumonia, with areas of dulness or slight loss of resonance) continued up to February 7. After this date there remained only signs of bronchitis. The general condition improved progressively, keeping pace with the condition in the chest. A blood examination made February 11 showed 85 per cent. hemoglobin (Gowers), 5,460,000 red blood cells and 7,800 leukocytes. Under the influence of pulmonary radiotherapy and heliotherapy, the patient seemed to be entering on convalescence.

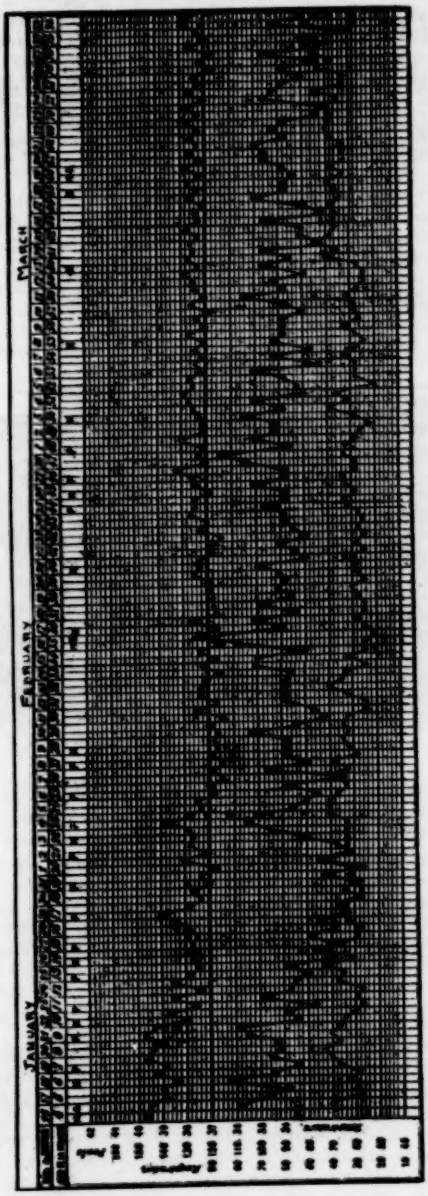

Figure 4

The expectoration remained fetid to the middle of February (sixth injection of novarsan), the spirilla increased to the same time, and then diminished, disappearing with the fetor of the breath about March 8 (tenth injection of novarsan).

CASE 5.—Deh . . . F., aged 27 years, infantryman, subject to winter bronchitis, was seized suddenly Feb. 5, 1918, with several chills, some associated with actual chattering of the teeth. There was headache, nose bleed, nausea and vomiting on five occasions. February 6 and 7 he had colic and three or four liquid stools; slight cough; no expectoration.

The patient entered the hospital February 13. Temperature, 38 to 39.5 C.; pulse, 100; respiration, 30; nothing abnormal on physical examination. February 14 blood cultures were sterile, no agglutination with dysentery bacillus, typhoid or paratyphoid, but the spleen was palpable. February 15 cultures of the urine and Diazo reaction were negative. On that day, however, the patient began to raise reddish and then rusty expectoration, and examination of the chest revealed dulness at the right base with rough respiration. A few moist râles were heard in this area February 17. The expectoration remained

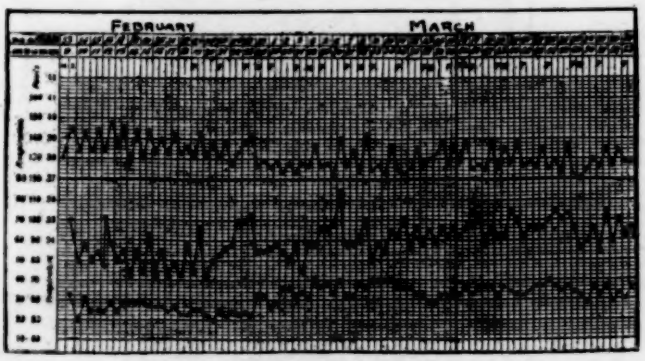

Figure 5

moderate, inodorous, at times mucopurulent, but always contained more or less blood. The temperature remained elevated. New agglutinative tests were made, likewise fresh cultures from the blood and urine; these threw no light on the diagnosis. Because of the intoxicated and prostrated condition of the patient, repeated intravenous injections of peptone were carried out every other day.

February 27, while the condition was still unimproved, the patient began to expectorate a brownish sputum with a pronounced odor of lactic acid. Microscopically, the presence of numerous spirilla (Figs. 7 and 8) was revealed. February 28, along with peptone and wet packs for the chest, a series of intravenous injections of novarsan (30, 45, then 60 cg.) was carried out every five days. In addition, injections of creosote were given, as well as heliotherapy and cod liver oil. During March the pulmonary symptoms continued to remain very slight, the expectoration remained red or brown and still contained numerous spirilla March 16. After March 23 (fifth injection of novarsan) it became paler, more like an ordinary mucous expectoration and contained fewer pathogenic bacteria. The general condition improved slightly. The temperature did not become definitely normal until after March 12, that is until after nine injections of neoarsphenamin. The patient received a tenth injection March 18 and left the hospital entirely convalescent June 21, 1918. Frequent search for the tubercle bacilli in the expectoration was always negative.

Case 6.—Van P. H., aged 27, artilleryman, was seized March 12, 1918, with a stitch in the left side and dyspnea. There was fever, cough, abundant expectoration and epistaxis. March 16 the expectoration became fetid. March 20 the patient entered the hospital. Examination of the chest at this time showed slight dulness at the right base, sonorous and sibilant râles disseminated throughout the two lungs, and medium moist râles in the outer part of the left chest. Physical examination was otherwise negative. The temperature ranged from 37.5 to 39 C. The pulse was accelerated (96); respiration was a little rapid (24). The sputum, examined March 21, was rather purulent, greenish, moderately fetid and contained neither tubercle bacilli nor spirilla. Wet packs were applied to the chest and creosote was administered daily by enema.

March 22 a fresh examination of sputum showed some spirilla. Arsenical treatment was begun. Thereafter the spirilla became more abundant and the fetor of the expectoration increased sharply. At the end of March the disease was still at its height and the general condition remained serious. March 30

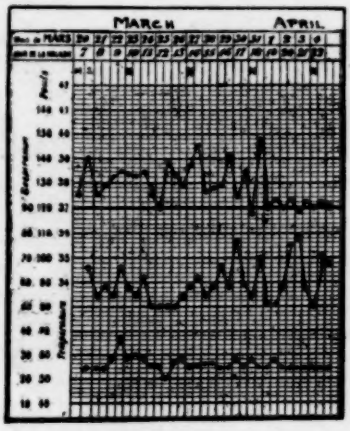

Figure 6

the expectoration contained no more spirilla. March 31, 60 cg. of novarsenobenzol was given intravenously. After this last injection the general condition of the patient improved; the fever disappeared. For twenty-four hours the patient expectorated more freely. The odor had nearly disappeared from the sputum; there were no spirilla. The soldier left the hospital entirely well April 22, 1918.

In examining the sputum collected in sterile petri dishes after careful rinsing of the mouth, we found in the first four cases and in the sixth, a spirillum, which, although rather variable in its size, presented morphologically an appearance which permitted of its recognition with a little experience. It stained very badly with the basic coloring matters ordinarily used in bacteriology. In order to bring it out, one must have recourse to some mordant. We used the method of Fontana, which gives excellent impregnations when the preparation is spread in

a sufficiently thin layer, or a procedure described by one of us,[4] which consists of the use of formol and chromic acid as mordants, staining by formalized violet and reinforcing by Lugol's solution. After this treatment the spirilla are of a brownish-black color (Fontana) or of a bluish-black (Spehl) on the colorless background of the preparation. Their dimensions are variable. Their length varies from 8 to 12 microns, their thickness is about that of Vincent's spirillum; it is a little greater in the preparations stained by Fontana's method. The extremities are tapering and appear not to carry flagella, at least we have never seen them in our preparations. The convolutions are short, sometimes regular, generally irregular, some being much less well marked than their neighbors, which results, perhaps, from the circum-

Fig. 7.—1. Spirilla of fetid bronchitis, found in the expectoration of all our patients. (Drawing made with camera lucida, ×750.) 2. Spirilla of Vincent. (Drawing made with camera lucida, ×750.)

stance that the parasite generally takes on a sinuous form, each one of sinuosities including a greater or less number of convolutions. The usual number of convolutions is from seven to eight for the adult forms. Exceptionally, we have counted as many as ten and eleven. What seems to us especially characteristic from the point of view of form is the coincidence of elbows or undulations of large size and of short, crowded convolutions, which gives to the spirillum a particularly tortuous character (Fig. 7). The accompanying figure drawn with the camera lucida, reproduced fairly faithfully the appearance of the preparation.

4. Spehl, P.: Procédé de coloration des spirilles par le violet-formolé, Compt. rend. Soc. de biol. **81**:305, 1918.

In examining these two figures, one may see morphologic differences which distinguish clearly the spirillum of fetid bronchitis from the spirillum of Vincent.

So far as we know few spirochetes take this aspect. With some experience it is easy to differentiate the micro-organism which we have found in our cases of bronchitis from the two known spirilla of the buccal cavity, such as the spirillum of Vincent (*Spirillum refringens*) and *Spirochaeta dentium*). We do not, then, wholly share the opinion of Castellani and Violle, each of whom insists on the extreme polymorphism of the spirochetes which they have described. Indeed, we have succeeded in finding, alongside of these forms, which we regard as characteristic, spirillum of aberrant form, sometimes in great numbers.

Our first observation was made prior to these two publications. It dates back to April, 1917. Between April, 1917, and July, 1918, we observed ten other cases among about 5,000 patients who passed through our first line hospital during this period. In our eleven patients there was also bronchitis, or more frequently bronchopneumonia, as in those of Castellani and Violle, but the clinical appearance and evolution differed at several points from the affection described by those authors.

In nine of our eleven cases the disease was primary. It seized the men in good health, and generally had a sudden onset, characterized by one or more chilly sensations or shaking chills. The patient suffers from general malaise, headache, pains in the extremities and loins. The spleen was palpable in two instances. The cough generally produced pain in the chest without an actual stitch. In one case there was epistaxis, scanty but repeated. In several cases the pulmonary symptoms were very slight in the earlier days of the disease, which appeared rather as a general affection than as a malady of the respiratory tract. Even after the symptoms related to the respiratory tract have developed further and taken a prominent place in the picture, there may, at the outset, be nothing characteristic, the local signs being those of an ordinary bronchitis and the expectoration mucopurulent, frothy, without special morphologic or bacteriologic characteristics. But there is one characteristic common to all the cases; namely, that the disease never shows the least spontaneous tendency to recovery.

The fever, generally irregular, is at the outset elevated, or tends progressively to rise, the general condition becomes aggravated, the patient loses strength, is feeble, out of breath on the least effort, while the face and extremities assume a more or less marked cyanosis. In the chest the signs of bronchitis, indefinite at first, become clearer and more extensive; in the posterior parts of the lungs zones of dulness or diminished resonance develop, localized commonly at the bases; the

expectoration becomes more and more abundant; it is slightly aerated, purulent rather than mucopurulent, of a greenish yellow color, and — an important sign — it becomes fetid while the breath takes on a repulsive odor. This fetor of the breath and expectoration has been manifested in all of our patients. In the grave cases it existed at the outset and had a cadaveric character. With the spasms of cough it spread to some distance, and distressed the patient's companions in the ward at a distance of several meters. Sometimes the air of the whole room was poisoned.

In the milder cases the fetor was not evident in the early days of the disease, or was too slight to attract attention. It was only after several days that it was perceived by the hospital personnel, or sometimes by the patient himself. But, as has been said, it always appeared at some period in the evolution of the malady, generally precociously. This characteristic is all the more notable in that it is not pointed out by Castellani or Violle.

Fig. 8.—Spirilla in sputum in Case 5. (Camera lucida drawing, ×750.)

The expectoration of our patients is distinguished further from the bronchial secretions of patients observed by Violle. It was hemorrhagic in only one case. In this case it had the characters of glary, viscous masses with a homogeneous rose violet color. Later, it took on a brownish hue. In another patient, the expectoration was rusty in the first days of the disease, but became rapidly mucopurulent. Apart from these two cases the bronchial secretion of our patients always had the color and consistency described in the brief résumé of the history of six persons attacked by the primary form of the disease. Thus, in Case 5, which is, by the way, the only instance of expectoration regularly bloody in the early days of the disease, we found, for the greater part, forms a little different from those which have been described, generally shorter, less tortuous, a little thicker, and a little less tapering at the extremities (Fig. 8).

Alongside of these there were, however, fewer spirilla having the characteristics of those which we found in all our other patients. It is difficult to express a definite opinion as to the question whether the micro-organism represented in Figure 8 is different from that shown in Figure 7 (1).

In one of the patients, where the affection was secondary (Case 7) and in whose expectoration the spirilla were particularly abundant, there were, alongside of the ordinary forms, a certain number of spirilla which, from their appearance, recall the spirillum of Vincent. In this case, which was one of particular gravity, the expectoration was extremely abundant and of a repulsive fetor. Possibly, the bronchial lumina had been invaded secondarily by the micro-organisms of the mouth, which in this very sick man, may have found in the bronchial secretions an excellent culture medium.

An interesting point is the greater or less abundance of spirilla in the expectoration. In certain patients they are very abundant. They may be found, so to speak, in every field of the microscope, sometimes several in each field, even in very thinly spread preparations. But it is not always thus. In other instances the micro-organisms are much rarer. One must sometimes examine a large number of fields before finding one. In a general way, one may say that the gravity of the affection is in direct proportion to the number of the spirilla. In the fatal cases they are as abundant in the bronchial mucus as is the spirillum of Vincent in the detritus which covers the ulceration of the disease tonsil.

It has seemed to us that the more numerous they were, the more fetid was the breath and the expectoration, and it was because in our first patient this fetor was very striking and the number of spirilla great, that we thought immediately of seeking a relation between the one and the other, and recognized the possibility of the pathogenic rôle of the spirillum. On the other hand, when, under the influence of treatment, the disease tends toward recovery, improvement goes hand in hand with the diminution of the spirilla in the secretion, a diminution which becomes evident even when the general characters of the expectoration, excepting the odor, have as yet shown no change.

In summary we found in our six patients with a primary fetid bronchitis a spirillum which seems to us to be the same in all cases, except for the circumstance that in Case 5 it was associated with a second form.

From a clinical point of view, the affection is sufficiently characteristic to permit its recognition after several days of observation at least. That which distinguishes it, as has been said above, is the high remittent fever, which has no tendency to fall spontaneously, despite a severe regime (rest in bed, liquid food, wet packs to the thorax, expec-

torants or balsamics) progressive loss of strength, dyspnea on the slightest effort, more or less well marked cyanosis and the peculiar character of the breath and expectoration. All of our last cases have been recognized clinically before confirmation from the laboratory. As a matter of fact, we hold that the only possible confirmation is the habitual presence in the sputum of a spirillum with the staining characteristics and the form described.

When one examines carefully the bronchial expectoration of patients affected with acute or chronic inflammation of the bronchi or of the pulmonary tissue, one may discover occasional spirilla, but this is rather an accidental event. The micro-organisms are rare, and have not, from the standpoint of their shape, the characters that we have found constantly in all of our cases. The question which arises is as to what is the etiology of this affection and how it spreads. Is it a malady analogous to whooping cough or measles, whose parasite exists only in those who are affected with or in the period of incubation of the disease, or must it be placed alongside of pneumonia whose micro-organism is to be found in the upper respiratory tract of healthy subjects. Our two cases of secondary fetid bronchitis speak in favor of the second alternative. The first case was that of a man, who, having a gastric ulcer, was obliged to undergo a gastro-enterostomy because of persistent hemorrhage at a time when his resistance was low. Immediately after the operation, there was fever, attributable to a pneumonia at both bases, which from the outset was characterized by a fetid breath and mucopurulent expectoration rich in spirilla. This man had been in the hospital for four weeks, in a ward where no similar case had been treated previously. The affection pursued its course to a fatal issue in twelve days.

The second case was that of a soldier who had been gravely intoxicated by dichlorethylsulphid. The bronchopneumonia produced by the poison took on an infectious character on the fourth day. Little by little, the expectoration became fetid. This phenomenon led to a microscopic examination of the sputum which revealed the presence of very numerous spirilla, but, curiously enough, the spirilla particularly abundant in these two extremely grave and fatal cases, after a short course, were the same in their staining affinities, their dimensions and their form, as those found in the cases of primary bronchitis. We are, therefore, led to conclude that the upper respiratory tract of these two men, normal up to that time, harbored the specific spirillum, and as there is little reason to believe that they were in a period of incubation, since the first had been cared for at the hospital for more than four weeks, we are rather led to conclude that the spirillum of fetid bronchitis may exist as a saprophyte in wholly healthy individuals. In like manner, we may add, that although our patients suffering from the

primary affection were never isolated, and although they lived for considerable periods in the common wards, we have never observed an instance of contagion. The affection is, however, relatively rare, since we have had only eight cases,[5] as against eighty-three of pneumonia and bronchopneumonia treated during the same period.

The history follows of two cases of secondary bronchitis:

Case 7.—J. O. R. . . . E., aged 29, in the auxiliary service, for a year has suffered from intermittent gastric disturbance. September 8, 1917, he was seized by vomiting, which continued during the following days and was preceded by pyrosis. Hematemesis occurred on the evening of September 20 and necessitated his entering the hospital on the twenty-first.

On examination, a diagnosis of gastric ulcer was made, and the patient was treated by suitable diet, calcium chlorid and several intramuscular injections of peptone. His general condition being sufficiently improved, he underwent an operation for gastro-enterostomy (ether narcosis) October 25. With the exception of several attacks of vomiting the results of the operation were good.

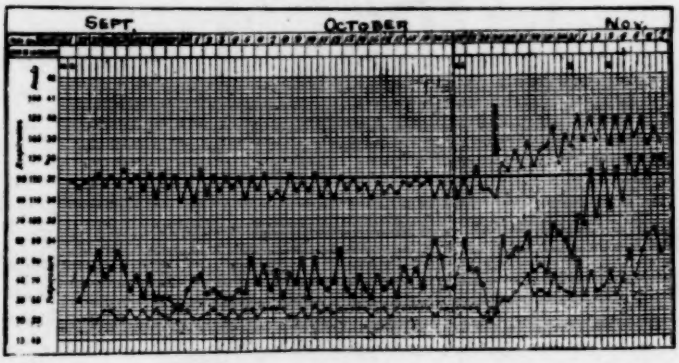

Figure 9

October 27 the patient began to expectorate a little mucus. The cough brought on vomiting. October 28 and 29 the vomiting ceased, but expectoration became mucopurulent and increased in quantity. October 30 the expectoration began to give forth a slightly disagreeable odor, but became clearly fetid on the following day, and was of a frankly purulent character. A microscopic examination made October 31 revealed numerous spirilla. The patient was immediately transferred to a medical ward and received an intravenous injection of 45 cg. of novarsenobenzol. Examination of the thorax revealed dulness at the bases of the lungs, especially the left. In places there was pectoriloquy and blowing breathing. Dyspnea was marked and prostration striking. Warm moist packs were applied to the chest. November 1 the fetor increased and this increase continued until his death. The pulmonary symptoms persisted. Digitalin was administered. November 3 a few fine râles appeared in the middle of the left lung in addition to the râles of bronchitis, and another dose of novarsan was administered. November 4 and 5, the general condition improved and intravenous injections of peptone were given.

5. In April and May, 1918, we had occasion to care for three new cases, and to bring the patients to recovery by intravenous injections of novarsan.

November 6, the symptoms became aggravated. The spirilla were always very abundant; the fetor of the breath was evident in the ward; dyspnea was intense; the patient was given oxygen through a nasal tube, and camphorated oil, strychnin and tartar emetic. November 7 there was bilious vomiting. The patient died at 5 p. m.

At necropsy the lungs showed a generalized edema, patchy bronchopneumonia and miliary abscesses, *in the pus of which the pathogenic spirilla were found.*

Case 8.—Baud . . . R., aged 25, infantryman, intoxicated by dichlorethylsulphid during the night of November 12 to 13, entered the hospital on the thirteenth suffering from burns of the face, eyes, scrotum and a general bronchitis. There was a little cyanosis of the extremities, but respiration was quiet and the pulse was not accelerated. Despite hot, wet packs to the thorax, the application of tincture of iodin and Dover's powder, the patient's condition became worse, the fever and pulse increased.

November 15 the respiration was blowing at both bases and accompanied by moist râles and a diminished resonance. Small doses of digitalin and ipecac

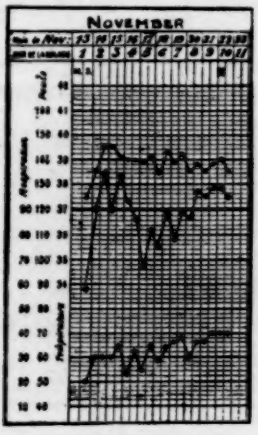

Figure 10

were given. The local signs, the exhaustion and cyanosis persisted, the expectoration became more abundant and took on a purulent character (November 20). Iodotannic syrup and creosote enemas were added to the treatment. November 21, the patient became definitely dyspneic. He was given oxygen continuously, strychnin and camphorated oil. November 22 the expectoration became fetid. Immediately, the patient received a potion of tartar emetic and an intravenous injection of 60 cg. of novarsenobenzol. Microscopic examination of the sputum showed many spirilla. November 23, his condition was desperate; there was pronounced fetor and numerous moist râles were audible in the chest. Death ensued in the morning.

At necropsy the lungs were generally edematous and congested and there were areas of disseminated bronchopneumonia. The glands of the hilum were enlarged.

If there were still doubt concerning the pathogenic rôle of the spirillum, it would be removed by the curative influence of the organic preparations of an arsenic base. This action is indeed not always

shown at the outset. Treatment must be long to control the disease definitely. If a series of intravenous injections of novarsenobenzol is made, in doses of from 45 to 60 cg., five or six days apart, a change in the clinical picture, rather slow in its development, may usually be made out. The condition, which, up to that time, has grown progressively worse, shows little by little, signs of an improvement, which, interestingly, affect first the elements characteristic of the affection. On the one hand, the fetor of the breath and the expectoration becomes less. On the other hand, there is a diminution in number, or even disappearance of the spirilla under the microscope. During this early period of arsenical treatment, the fever may remain tolerably high, and the local signs in the pulmonary apparatus are little influenced. It may even be that with the continuation of the arsenic treatment, the disappearance of the spirilla is brought about without amelioration of the general or local condition. This occurred in Case 2, which ended fatally. We have observed that the arsenical treatment acts better and more quickly the earlier it is begun.

This circumstance may be explained when one considers that the spirillum is far from being the only micro-organism to be found in the sputum which contains a particularly varied and abundant bacterial flora. The micro-organisms of which this consists probably add their injurious action to that of the spirillum. At the necropsy done in Case 2, both lungs were found dotted with miliary abscesses, of which the pus did not contain spirilla (tubercle bacilli were also absent), although the expectoration of the patient contained many before the beginning of arsenical treatment. It would appear that the lesions produced by the spirilla are severe, and that, invaded by the micro-organisms of secondary infection, they present little tendency to heal. This, perhaps, is the most distinctive character of the affection described in this article. Even after our patients had been rendered apyretic, and after their expectoration from being purulent had become mucous and free from spirilla, they continued to cough, and auscultation revealed signs of an attenuated but persistent bronchitis. We have had to have recourse to the combined action of balsamics, exposure to sun, and respiratory gymnastics definitely to overcome these sequels which always show an extreme obstinacy.

In certain cases we have added to intravenous injections of novarsenobenzol, peptone, administered intravenously every two days. It has seemed to us that this combination was more effective than treatment by arsenic alone (see especially Case 3).

We have termed the malady described in this article "fetid spirillar bronchitis," although, in reality, certain forms have from the outset taken on the clinical characters of a bronchopneumonia, and although at necropsy in the fatal cases there have been found either areas of

bronchopneumonia or pulmonary abscesses. The appellation "bronchitis" seemed to us to be more suitable because, at least in the primary form of the affection, the signs in the respiratory tract were very vague in the early days of the disease, and were those of an acute bronchitis. The examination of the sputum having proved that in addition to a spirillar infection there is added a considerable number of other micro-organisms, it is impossible to settle the question as to whether the extension of the bronchial inflammation to the pulmonary parenchyma is attributable to the spirochete or to the organisms of secondary infection. In the early days of the disease, when it is primary, the fetor may be absent or slight, and the spirilla very scanty in the expectoration. It may even be impossible to make them out at that time. Although the disease is not malignant, it is to be differentiated, however, from an acute bronchitis by a sudden onset with high fever, general phenomena, and especially a complete lack of tendency toward spontaneous recovery. After from several days to several weeks the patient loses his strength, becomes emaciated, his bronchitis merges into bronchopneumonia, the spirilla tend to become more abundant in the expectoration, while the fetor of the breath also becomes aggravated. All the patients observed by us were soldiers in the Belgian Army in the field, who had not lived in tropical countries, and had never been in contact with colonial troops.

For this reason, and for the others mentioned above, we have differentiated the affection from the two maladies analagous and yet distinct one from another, described, one by Castellani,[1] and the other by Violle,[2] both of which appear to originate in warm climates.

If, as we thought, the affection is autochthonous, it remains to be explained why we have had occasion to see a considerable number during the course of a year when, so far as we know, no disease of this sort had previously been described in temperate regions.

The most probable explanation appears to be the following: If the case is benign and remains benign (this eventuality we have not observed, but our observations do not permit us to exclude it), if it ends in recovery spontaneously or favored by treatment, there is considerable likelihood that it may be regarded as an acute catarrh of the upper respiratory tract. If, on the contrary, the malady becomes aggravated and lethal in its course, it will impress the uninformed physician as being an acute bronchopneumonia which, at a given moment, is complicated by pulmonary gangrene.

As a matter fact, the observations at necropsy in our fatal cases do not at first glance plead in favor of this point of view. One observes in the examination of the lungs postmortem, the presence of diffuse congestion and edema, areas of disseminated bronchopneumonia, sometimes multiple miliary abscesses, but no pulmonary gangrene.

During the summer of 1918, one of us had occasion to see a patient whose history would seem to bring new evidence toward the solution of the above problem. The following is a résumé of this observation.[6]

Case 9.—Berch, M., a soldier, aged 32 years, presented nothing abnormal from a hereditary standpoint. He had pneumonia at 17, acute dysentery one year ago. The history was one of sudden onset June 9, 1918, with general malaise and pain in the back. June 10 he had a stitch in left side in the region of the precordium, with dyspnea. Cough and expectoration appeared on the following day. On entering the hospital, June 13, he had a temperature of 37.2 C., pulse 100, and moderate dyspnea. His general nutrition might have been better. He was thin; his muscles were poorly developed. There was great prostration. The tongue, covered with a thick, whitish coat, tended to be dry. There was pyorrhea alveolaris. The digestive tract was negative. On examination of the chest, there was found diminution in resonance at the left base, and fine, localized crepitation in the left axilla. Throughout the remainder of the chest, dry râles of bronchitis were heard. The heart was negative. His arterial pressure was 16.9 (Pachon). The urine showed a trace of albumin. In the days following the temperature fell gradually, reaching normal June 22, while the signs of bronchopneumonia increased. The left base became dull, bronchial blowing breathing was heard. Later, June 20, the right base showed similar signs.

Moreover, June 23, fever recurred, the temperature rising to 38.2 C., descending gradually toward normal during the following days. June 29, the patient was afebrile, and remained afebrile until July 9, when there was a moderate new febrile paroxysm lasting several days. By July 12 there was again defervescence, of more than one week's duration without marked change in the condition of the bases posteriorly. The patient did not regain his strength. July 22 the fever again recurred, this time to remain. It was very irregular. The local signs did not vary. Expectoration became abundant; it was mucopurulent and fluid. Tubercle bacilli were sought for on various occasions without results. July 25 the patient expectorated sputum mixed with red blood about twenty times. This symptom caused us once more to incline toward the diagnosis of pulmonary tuberculosis, although examination of the chest revealed no lesions in the apices.

The appearance of a new symptom on August 5 definitely settled the diagnosis. On this day the breath and sputum were found to be very fetid. The nurse had made the same observation during the preceding days without thinking of calling our attention to it. The microscopic examination of the sputum revealed spirilla altogether analogous to those described by Spehl in several cases of fetid bronchitis. Nevertheless, despite the repeated administration of novarsenobenzol intravenously, the situation did not improve. August 16 the expectoration became hemorrhagic. August 17, the patient raised pure blood, and died on the eighteenth with abundant hemoptysis.

The necropsy, made by Dr. Colard, showed nothing notable in the heart or digestive tract. The spleen was increased in size and diffluent. No tubercle were found in the spleen, liver or kidneys. The right lung was adherent to the parietal pleura, and the three lobes were glued together by recent adhesions. There was diffuse bronchitis, congestion of the base; no tubercles. The left lung was bound over its whole surface to the parietal pleura by old, thick adhesions. In the upper lobe there was bronchitis without tuberculous lesions. The lower lobe was riddled with numerous cavities filled with foul pus. One of these, situated in the posterior and lower part, was of the size of a large nut. There were, moreover, numerous miliary abscesses. The lung itself was gangrenous almost throughout its lower lobe.

6. Nolf, P.: Un cas de gangrène pulmonaire à spirilles, Bull. de l'Acad. de méd. Par. **80**:657, 1918.

The interesting point about this case lies in the circumstance that it presented at first, the characteristics of secondary spirillar bronchopneumonia, the primary infection being here a grippal bronchopneumonia. There was, however, a clear tendency to pulmonary hemorrhages, and, indeed, it was as a result of an accident of this nature that the patient died. Barring this complication, nothing would have justified a clinical distinction between this case of secondary spirillar bronchopneumonia and the two cases observed above, but the necropsy showed the presence of an extensive gangrene of a lobe of the lung, which was absent, as has been said, in all the cases published by Spehl and me.

It has, therefore, been shown that one may find spirilla similar to those described by us in the expectoration of a patient in which an acute bronchopneumonia becomes complicated at a given moment with pulmonary gangrene. It is probable that this observation will be repeated when in other like cases, spirilla are sought by appropriate methods. It remains to be explained why, in the fatal cases which we have published previously, gangrene was nonexistent.

Two hypotheses may be considered: (1) In rapid diffuse forms, such as in Cases 7 and 8, death may occur before gangrene has had time to develop. (2) In the more circumscribed forms the evolution of which is less rapid, like Case 2, death at a late period seems to have been the result of secondary complications, as is proved by the complete disappearance of spirilla in the expectoration and in the pus of the abscesses—a disappearance brought about probably by arsenical treatment.

If the last hypothesis is sound, the sum of the observations heretofore made would allow us to ascribe to the spirilla a rôle in the production of gangrene.

In the present state of the question, and so far as our observations justify a conclusion, it would seem, then, that spirillar bronchopneumonia is a malady of temperate climes, and that it has probably been confounded up to the present time, with pulmonary gangrene consecutive to acute or chronic affections of the respiratory tract. Its micro-organism is probably a common inhabitant of the upper respiratory passages, particularly of the mouth and pharynx. In this connection it is interesting to observe that the last mentioned patient suffered from pyorrhea alveolaris at the time of his entrance into the hospital.

BOOK REVIEW

PULMONARY TUBERCULOSIS. By Maurice Fishberg, M.D., Clinical Professor of Medicine, New York University and Bellevue Hospital Medical College. Second edition, revised and enlarged. Illustrated with 100 engravings and 25 plates. Philadelphia and New York, Lea & Febiger, 1919.

The author of this work sets forth his object in the preface. The only drawback to this is that prefaces are rarely read, and the reviewer hopes that something may be gained by noting Dr. Fishberg's intentions here. He believes that physicians can and should do more to recognize phthisis in its earliest or pretuberculous stage; that institutional treatment is not the only effective way of handling the phthisical patient; available institutions would hardly accommodate 10 per cent. of the eligible patients should all wish to enter; even those who enter sanatoriums require treatment before admission and after discharge; careful home treatment may produce practically the same immediate and ultimate results as institutional treatment and is less costly to the patient and to the community. It would be well if these principles were inculcated into the minds of all classes of the community. It is useless for physicians alone to know them to be true. Since physicians will chiefly use the book, it is worth while to show whether the author has realized his aim in writing it. A critical reading brings the conclusion that the object has been very thoroughly attained. The subject matter is well subdivided and the different chapters have been skillfully treated so that in each one a clear idea is conveyed and at the same time no parts are disproportionately too long or too brief. Realizing that many who read the book have not had recent experience either in laboratories or clinical institutions, the author has adopted a simple, but clear, and on the whole, an accurate way of showing the present state of knowledge of tuberculosis and especially of consumption. The expert may not accept all the views held by the author, but even the expert must admit that the advice given, if acted on, would enormously advance the recognition and care of consumptive patients. Perhaps the pathologic details are discussed too briefly, but the matter will give a good starting point for any physician who wishes to take up the more advanced study, and there are useful references to recent original work in all the sections. The social relations are well described. In the chapter on symptomatology, the prevailing errors in practice and the most dangerous pitfalls for the inexperienced investigator are well and fully described. One can see on every page the author's close observation and careful study of clinical medicine as well as of the psychology of the tuberculous individual. The sections on physical diagnosis are particularly full, clear and accurate. Roentgenology is discussed well and clearly, and reproductions of roentgenograms are rather better than the average of their kind. The differential diagnosis is well worked up, and the complications are described well. Under prognosis, the various factors that are concerned are discussed with praiseworthy judg-

ment, while the sections on treatment are full and practical and the measures advised are such as are in favor with the most experienced specialists in and out of institutions. The illustrations, in general, are well chosen and well reproduced. The book has been made up carefully and is well printed. It should find a large audience, particularly among general practitioners.

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